Контактная сигнализация

с/к «Межклеточная коммуникация»

Лекция 4

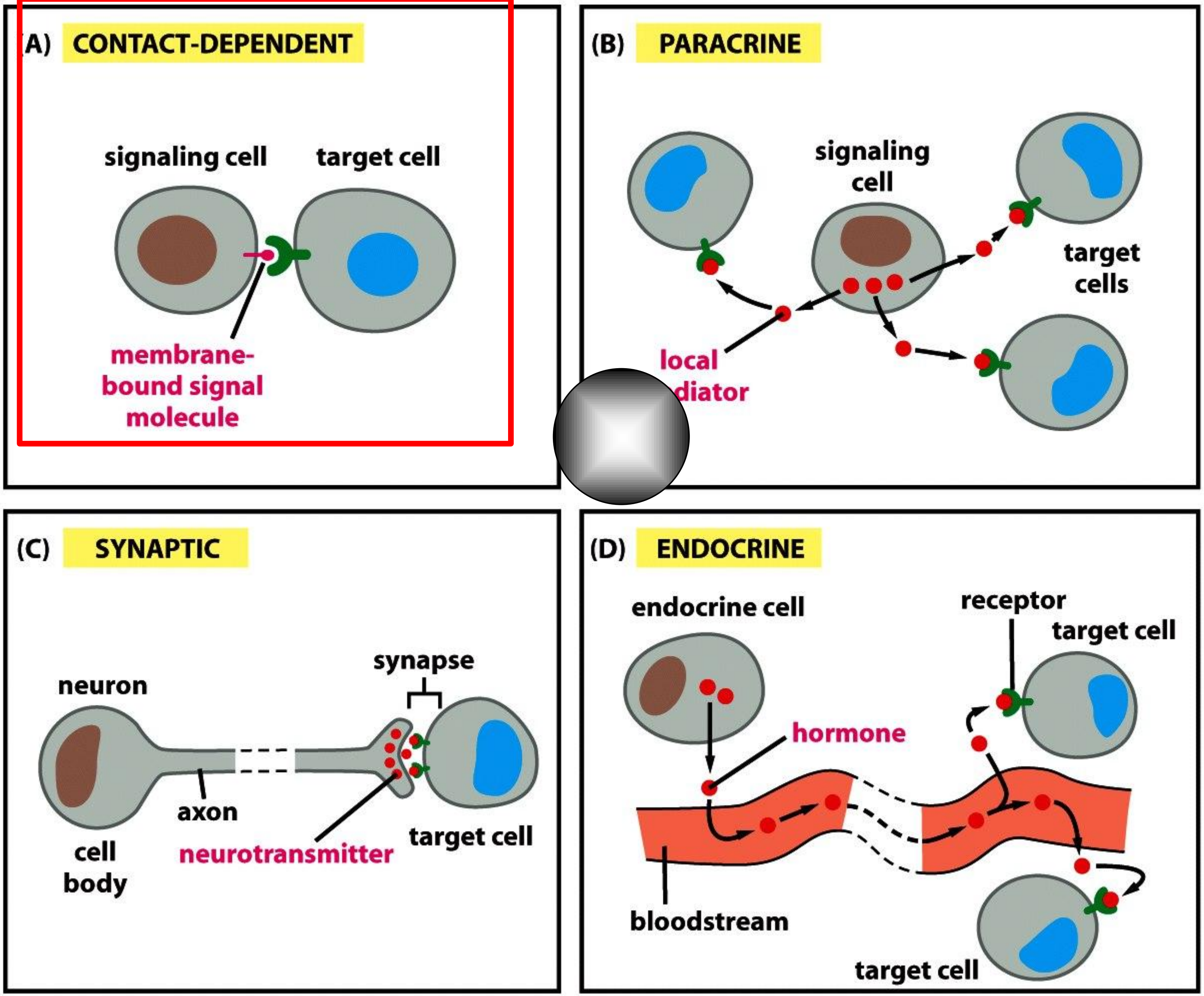
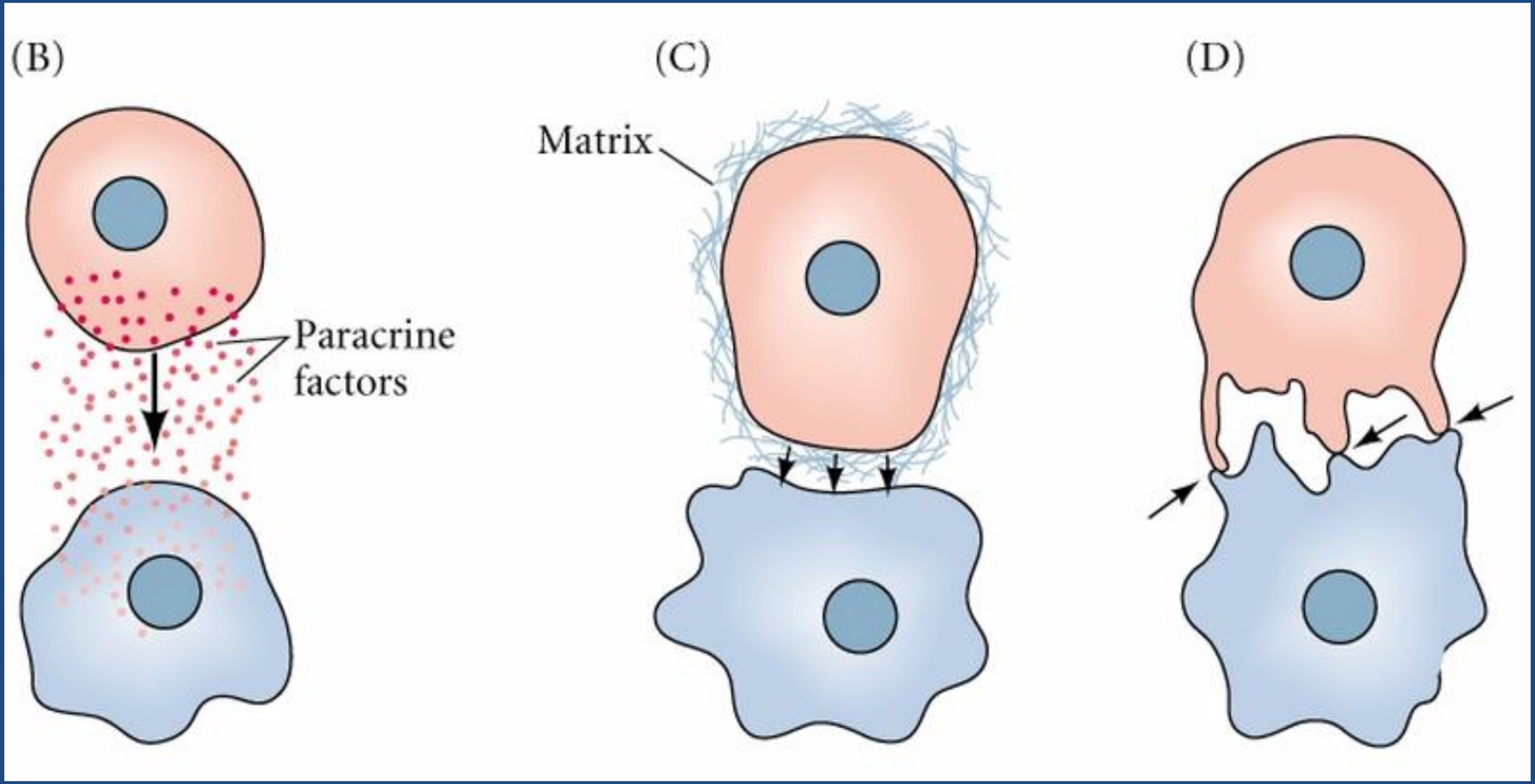


Figure 15-4 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Mechanisms of Inductive Signaling

Paracrine Signaling

Juxtacrine Signaling

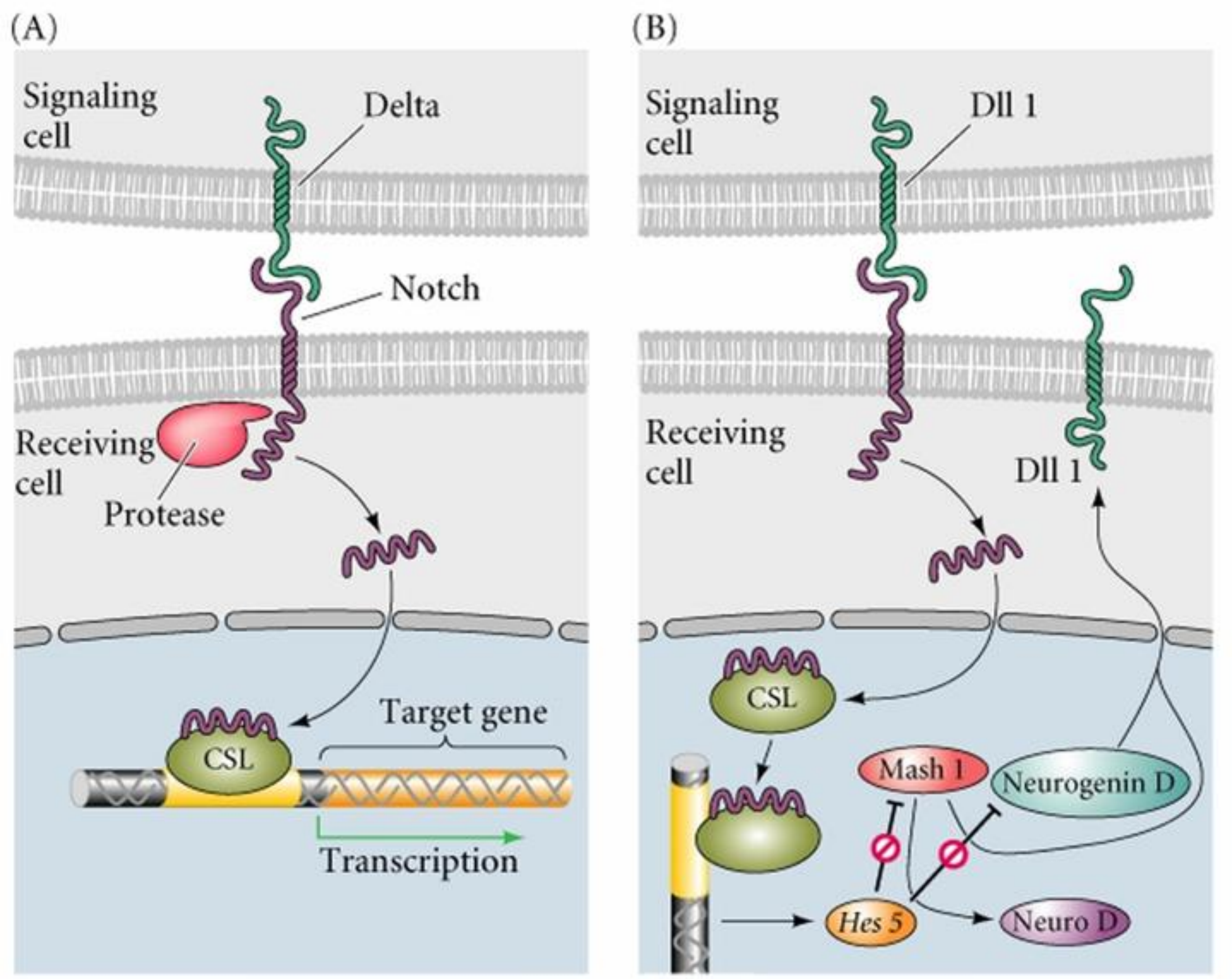


Juxtacrine Signaling

- How is this type of signaling different from paracrine signaling?

  - signal molecule is a protein that **resides in adjacent cell member**

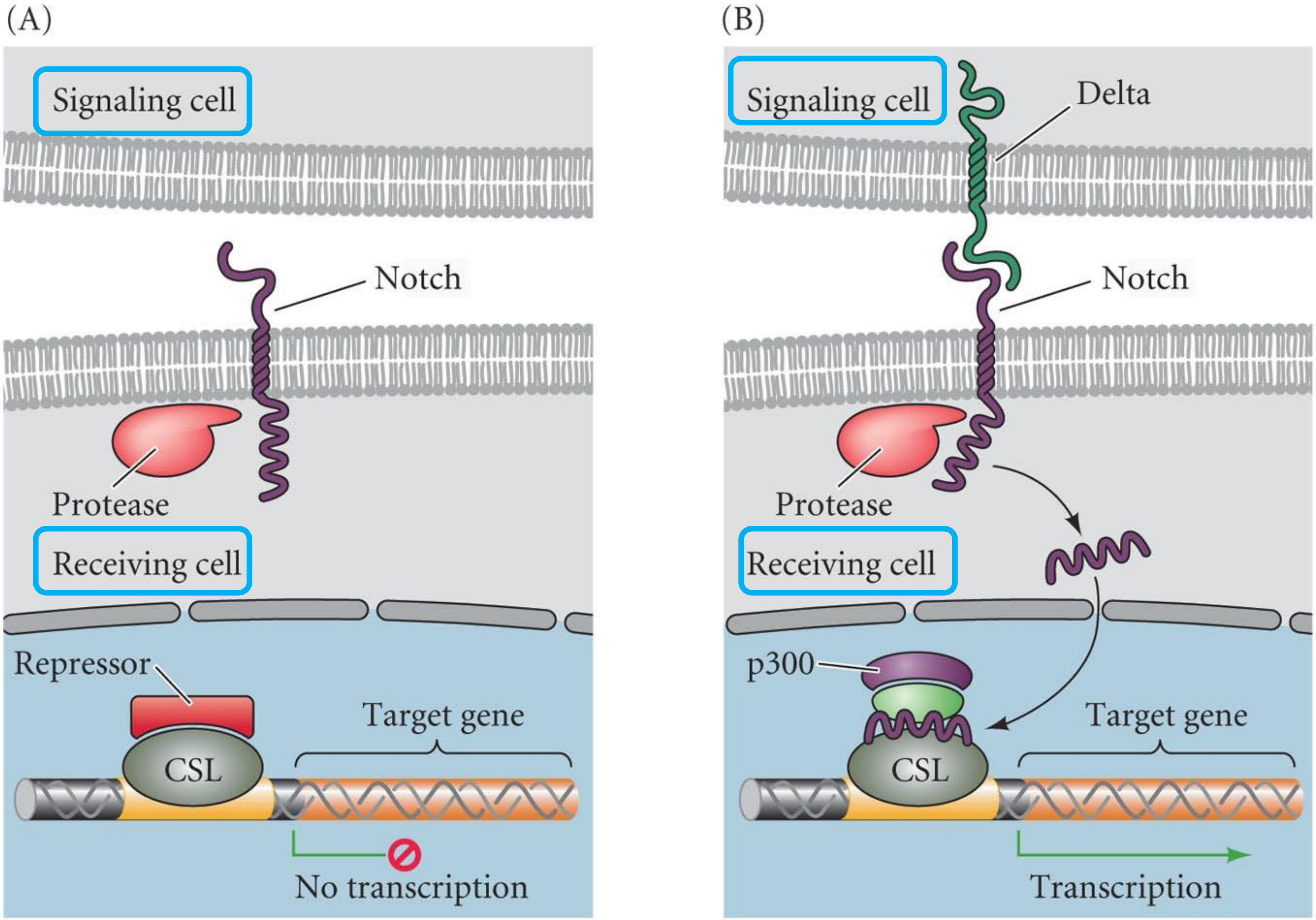
Juxtacrine Signaling: Notch Pathway



The core elements of the Notch signaling system

- Receptor family: Notch/lin-12, glp-1
- Ligands: (DSL) Delta, Serrate, Lag2, Jagged
- Processing: ADAMs (Kuz, TACE) and Secretases (Sel-12/presenilins)
- Downstream effectors: CBF1, Su(Hairless), Lag1 Collectively called CSL DNA-binding proteins (**CBF1/RBPJ-kappa** in vertebrates).

- Notch proteins and ligands contain **extracellular EGF** (Epidermal Growth Factor)-like repeats. Activation of Notch upon ligand binding is accompanied by proteolytic processing that releases an **intracellular domain of Notch (NICD)**.
- Notch is cleaved at least three times, releasing the transcriptionally active intracellular domain.



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Structure : transmembrane receptor

- Synthesized as a single precursor protein
- Cleaved in two during its transport to the cell surface.

Drosophila

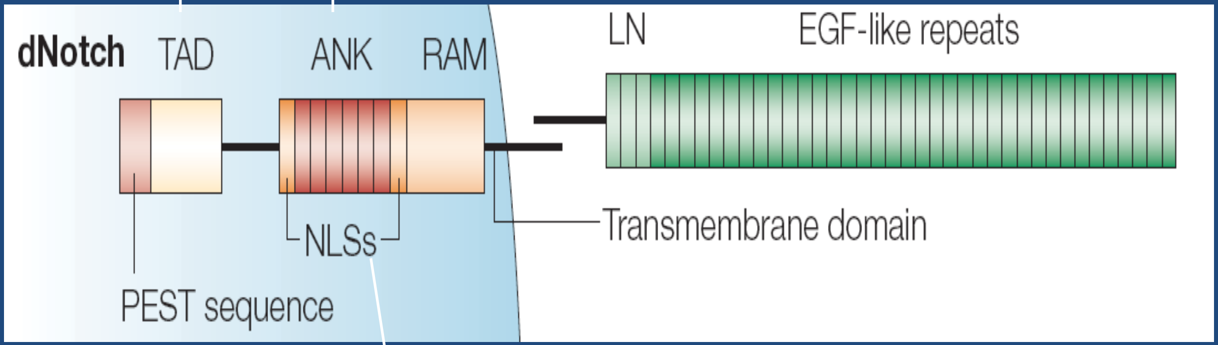
Notch receptor

Ligand

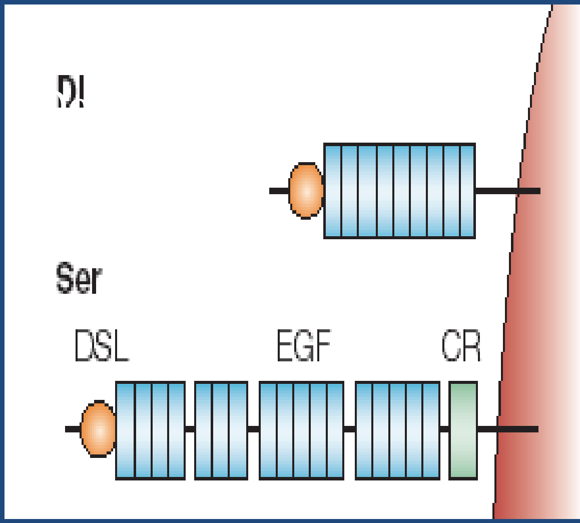
Transcription activation domain

CDC10 repeats

Lin12 repeats (cysteine-rich)



Nuclear-localization signal

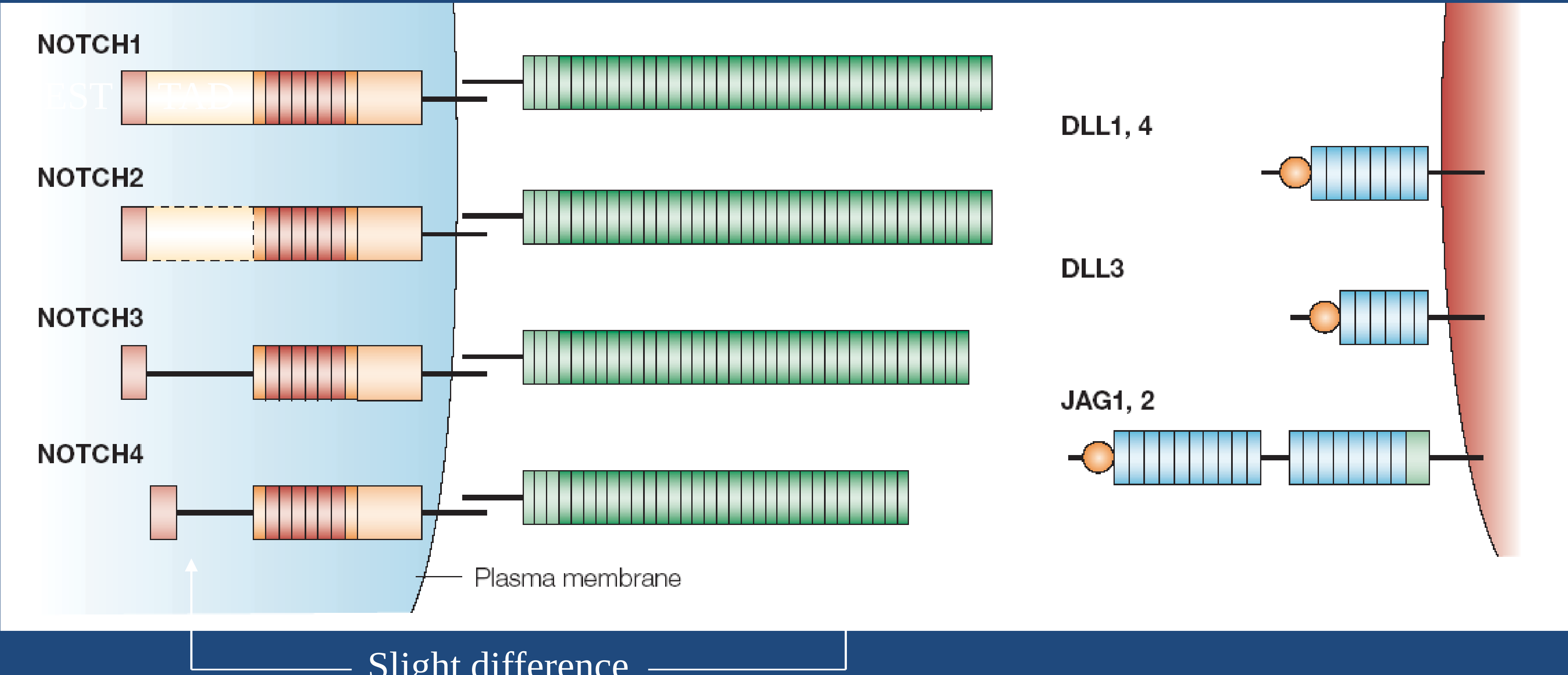


(Serrate)

Human

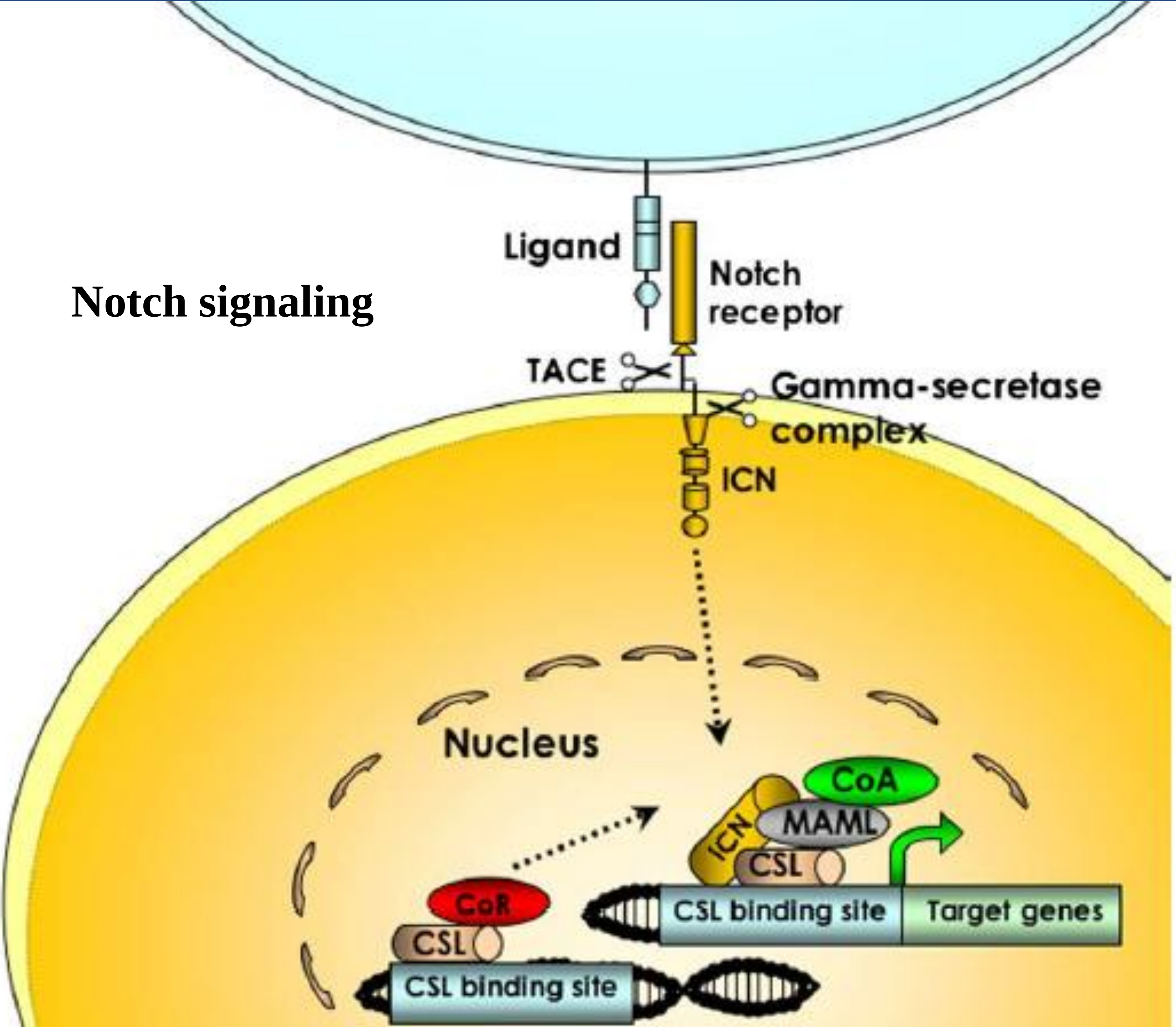
Notch receptor

Ligand



Slight difference

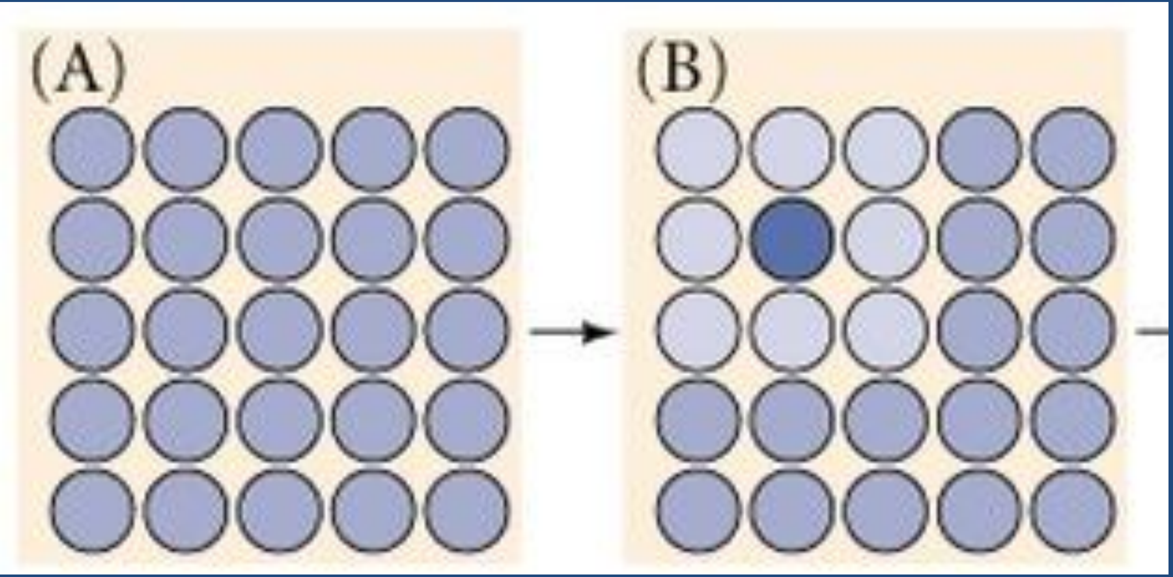
Notch signaling



Notch functions

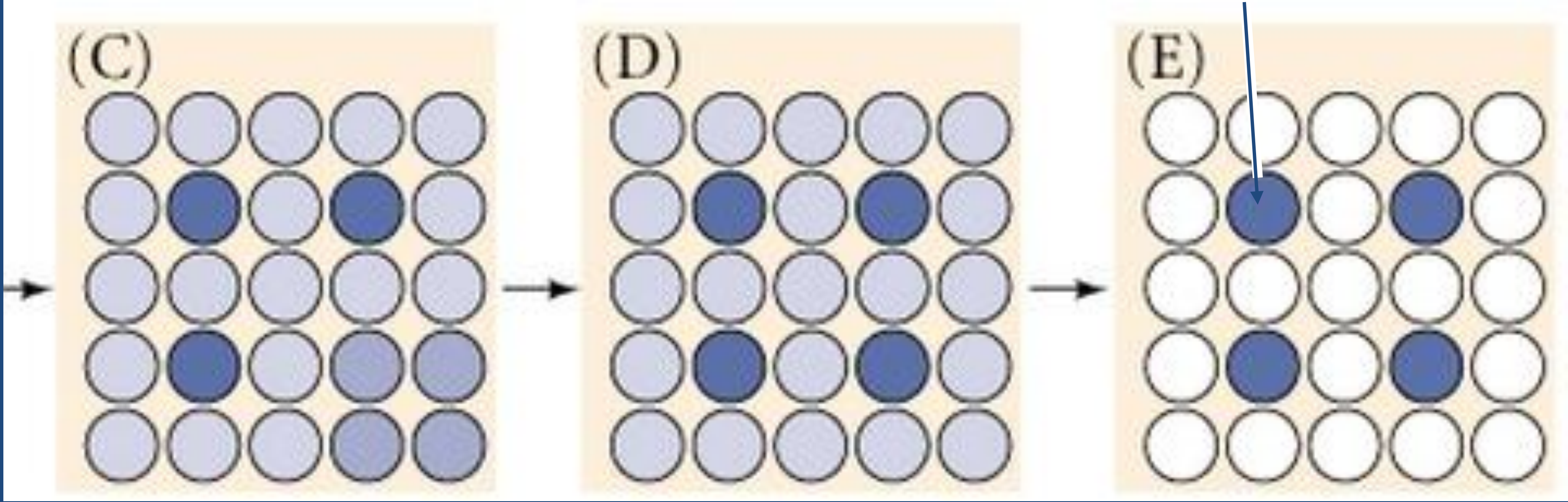
- The Notch signaling pathway is a fundamental signaling system used by **neighboring cells** to communicate with each other in order **to assume their proper developmental role.**
- Interaction between Notch and its proposed ligands initiates a signaling cascade that governs cell fate decisions such as differentiation, proliferation, and apoptosis in numerous tissue types.
- **Regulates:**
  - establishment of patterns of gene expression;
  - cell differentiation;
  - regulates binary cell fate choice;
  - maintenance of stem cell populations;
- **Function:**
  - Embryonic Development; Adult Self-Renewing Organs

Lateral Inhibition



Specification of neural precursor cells in *Drosophila* neurectoderm

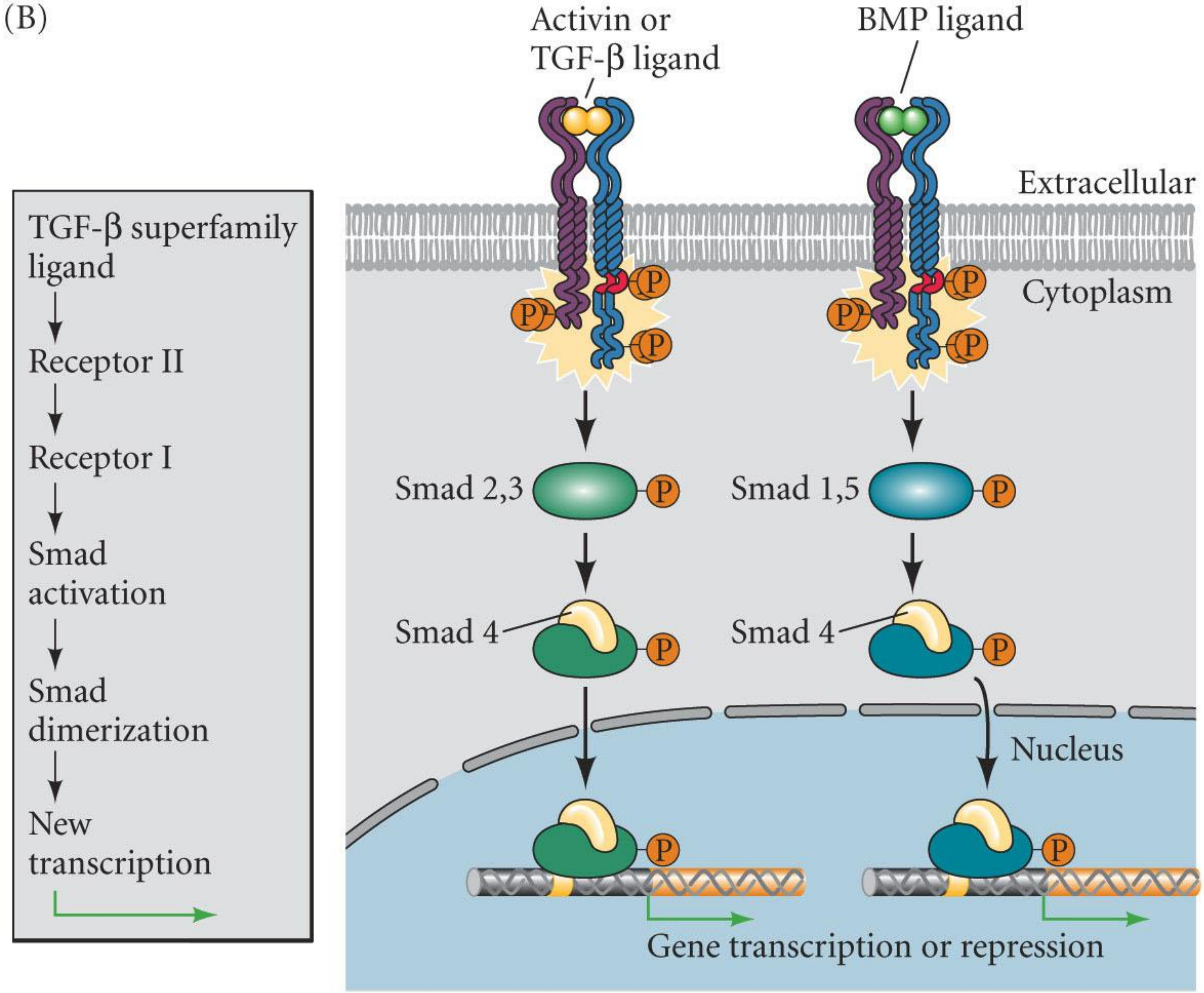
Blue cell becomes neural precursor – GMC; white ones remain epidermis.



Smad Pathway

- Mesoderm specification
  - TGFβ - activin, Vg1, nodal
- Ectoderm specification
  - BMP4, 7
- Dorsal specification (*Drosophila*)
  - Dpp

The Smad pathway activated by TGF-β superfamily ligands (Part 2)



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Smad Pathway Inhibitors

- Inhibitory Smads
  - Bind to smads 1, 5 or 2, 3 in the hypophosphorylated state & prevent interaction with smad4
  - Phosphorylation of smads 1,5, 2 & 3 disrupt inhibitory smad interaction and allow smad 4 binding
- Noggin
- Chordin
  - Bind to BMPs and prevent their interaction with receptors

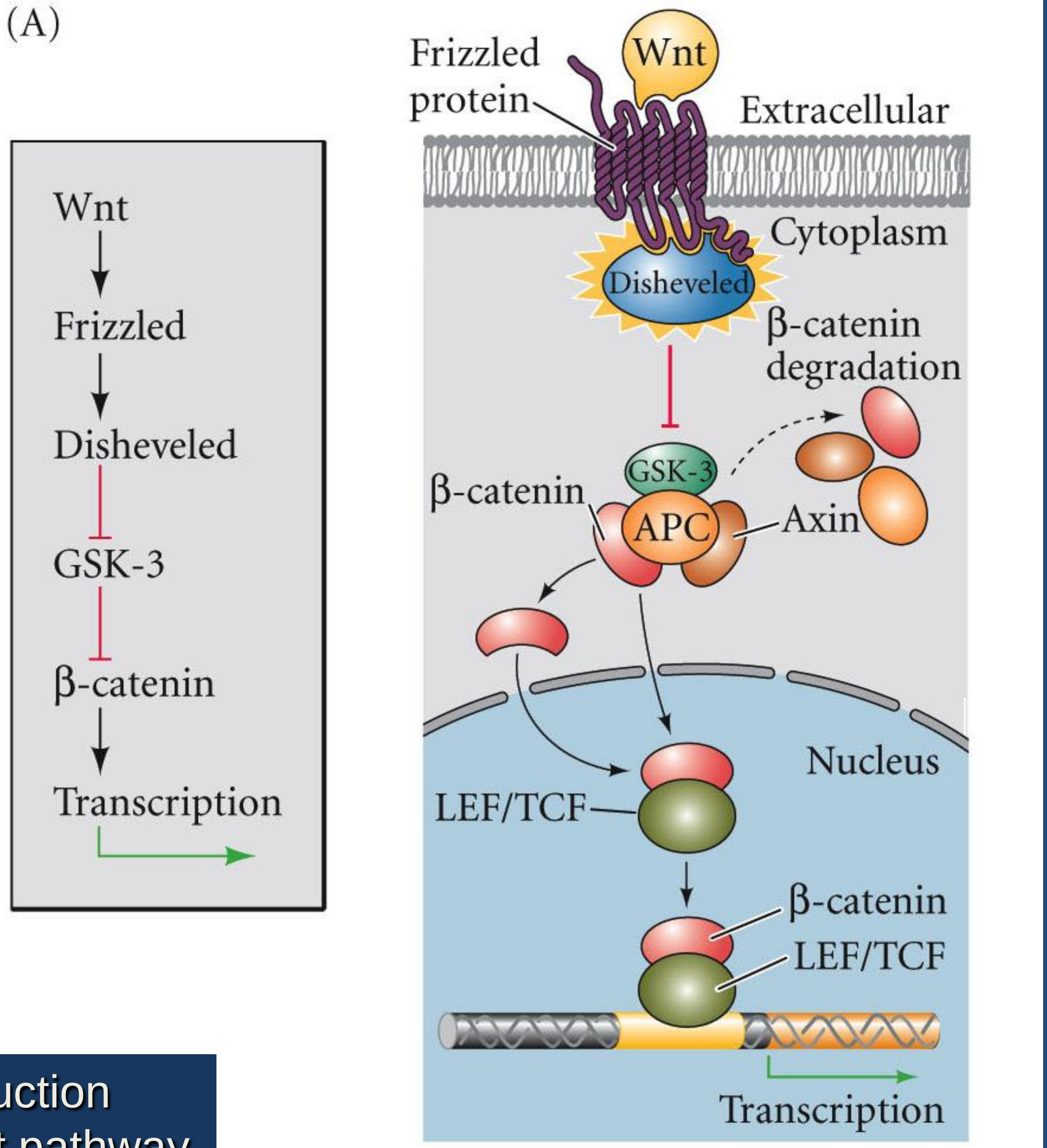
WNT- signaling

The WNT genes encode a large family of secreted *protein growth factors* that have been identified in animals.

In humans, **19 WNT proteins** have been identified with a conserved pattern of **23 or 24 cysteine residues**.

WNT signals are transduced through at least three distinct intracellular pathways,

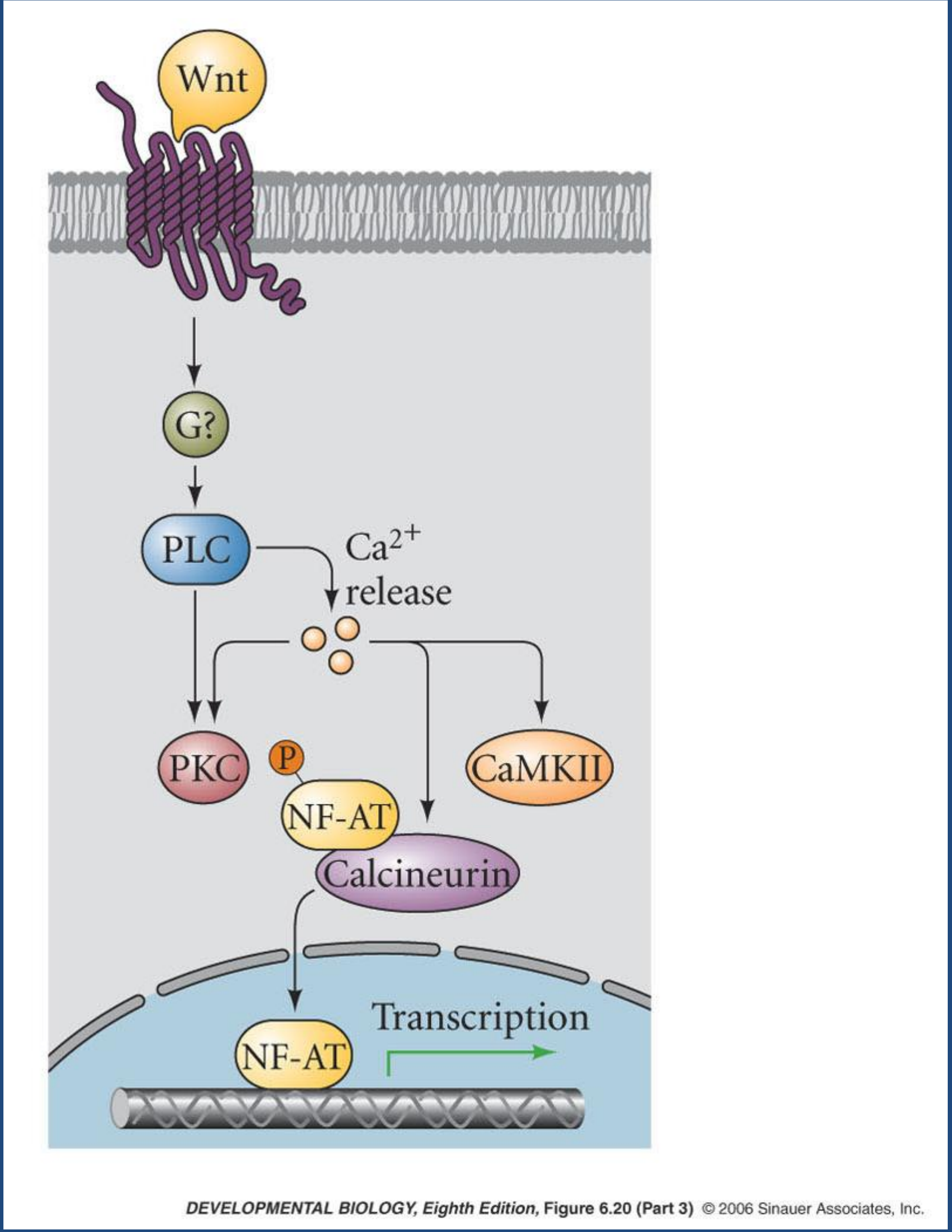
- the canonical WNT/ Ctnn-Beta (Catenin-Beta) signaling pathway
- the 'non-canonical' WNT/Ca2+ (Calcium) pathway,
- the WNT/PCP (Planar Cell Polarity) pathway.



DEVELOPMENTAL BIOLOGY, Eighth Edition, Figure 6.20

The Wnt signal transduction pathways – Canonical Wnt pathway

The Wnt signal transduction pathways – Calcium Signaling



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Cell Associated Signaling Molecules

- Integrins (receptor)
- CAMs (receptor)
- ECM (ligand)
  - Fibronectin
  - Laminin
  - Type IV collagen

- Notch Family (receptor)
- Delta Family (ligand)

- Eph Family (receptor)
- Ephrin Family (ligand)

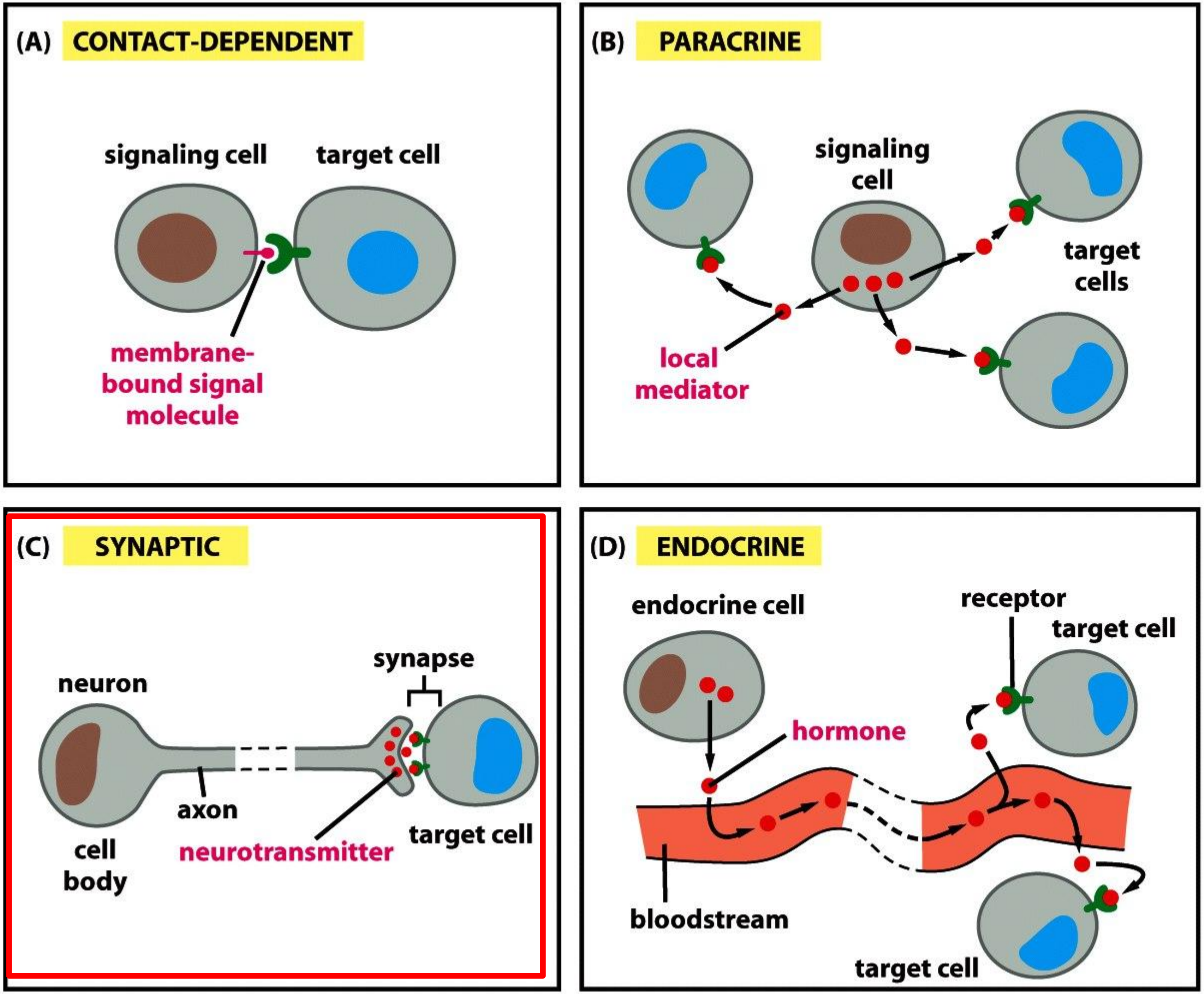


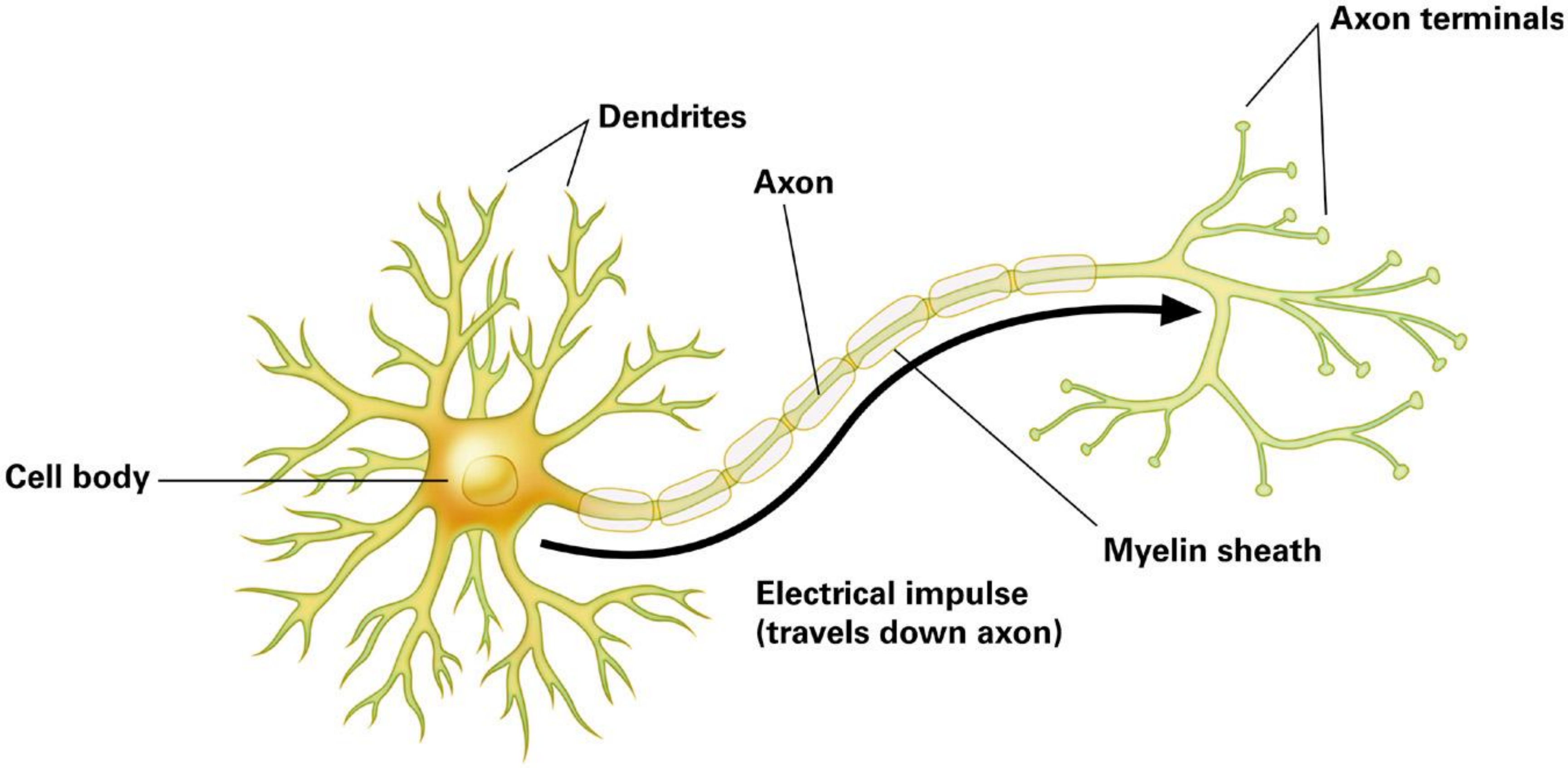
Figure 15-4 Molecular Biology of the Cell 5/e (© Garland Science 2008)

How Neurons Communicate

Communication
within
a neuron is
electrical

Communication
between
neurons is
chemical

The Structure of a Neuron



Ion pumps and ion channels maintain the resting potential of a neuron

- Every cell has a voltage (difference in electrical charge) across its plasma membrane called a **membrane potential**
- Messages are transmitted as changes in membrane potential
- The **resting potential** is the membrane potential of a neuron not sending signals

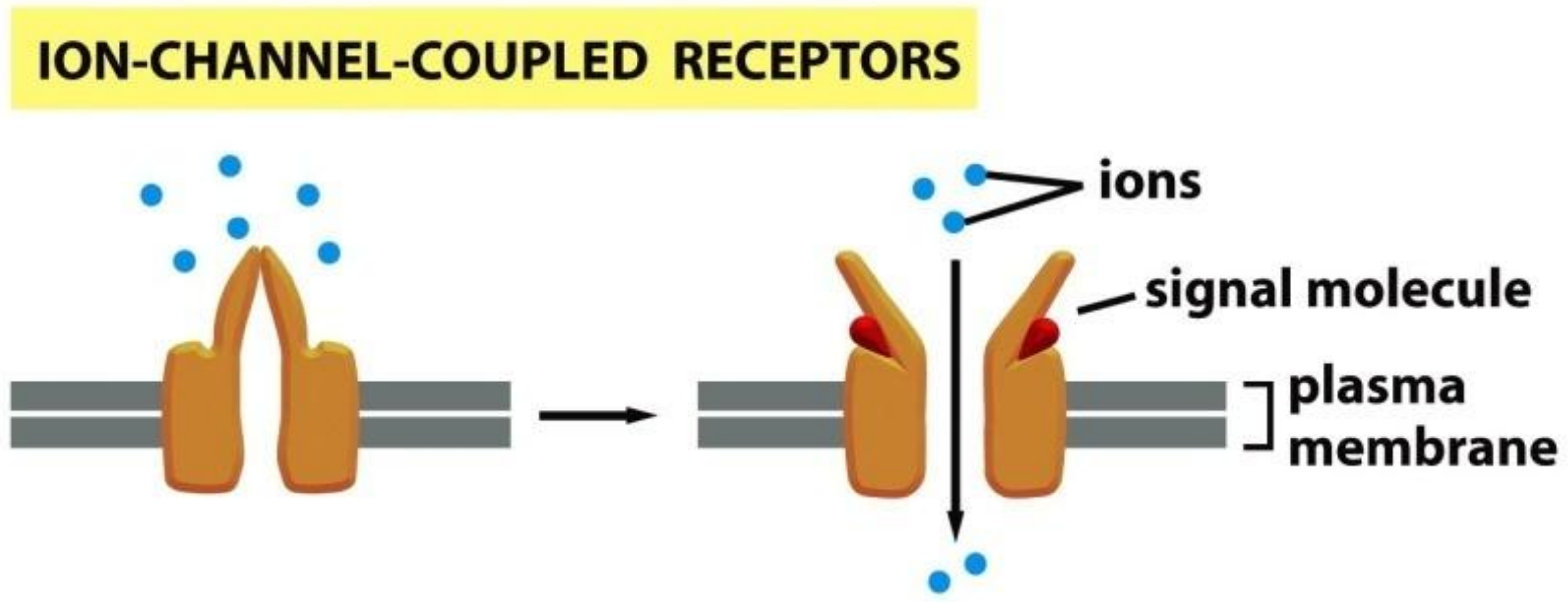
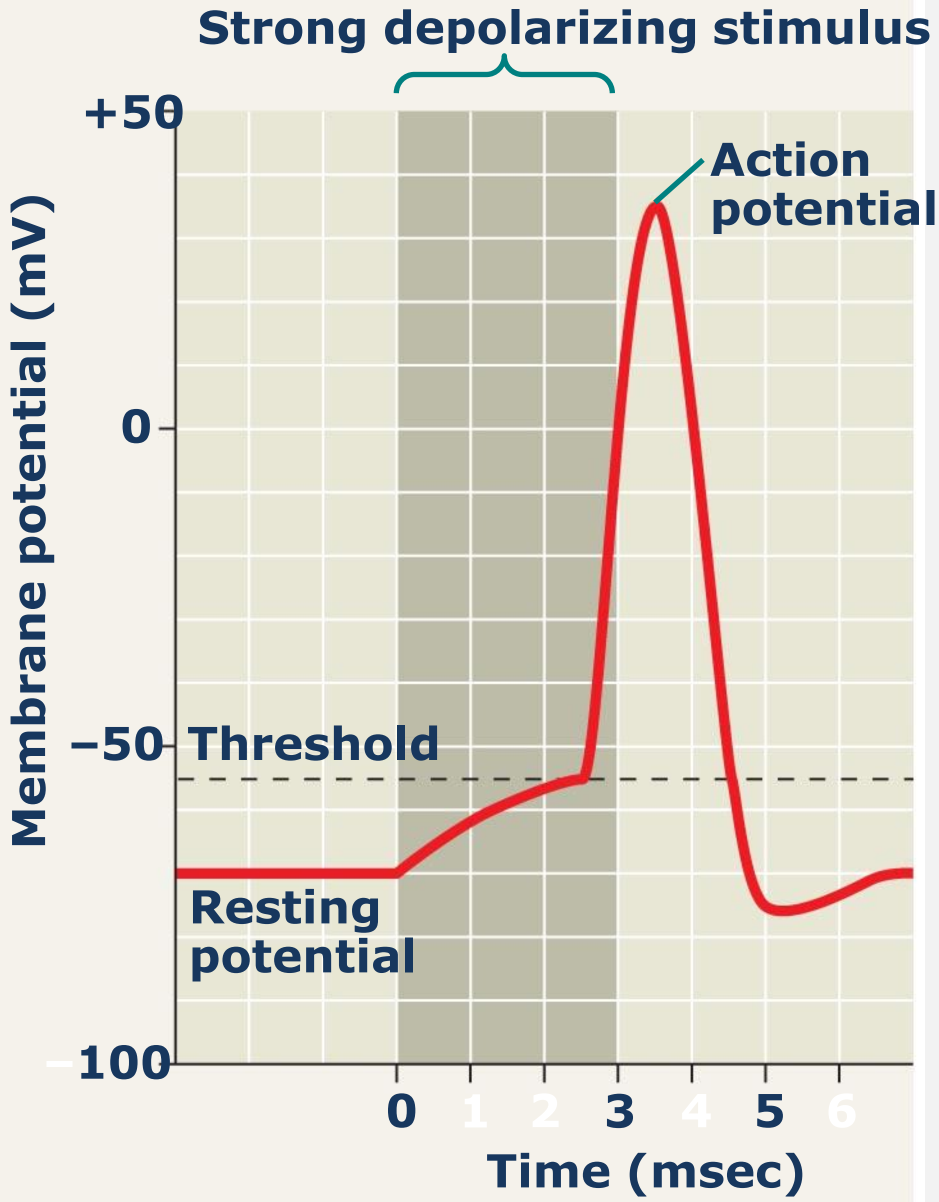


Figure 15-16a Molecular Biology of the Cell 5/e (© Garland Science 2008)

Voltage-gated Na^+ and K^+ channels respond to a change in membrane potential

When a stimulus depolarizes the membrane, Na^+ channels open, allowing Na^+ to diffuse into the cell

The movement of Na^+ into the cell increases the depolarization and causes even more Na^+ channels to open



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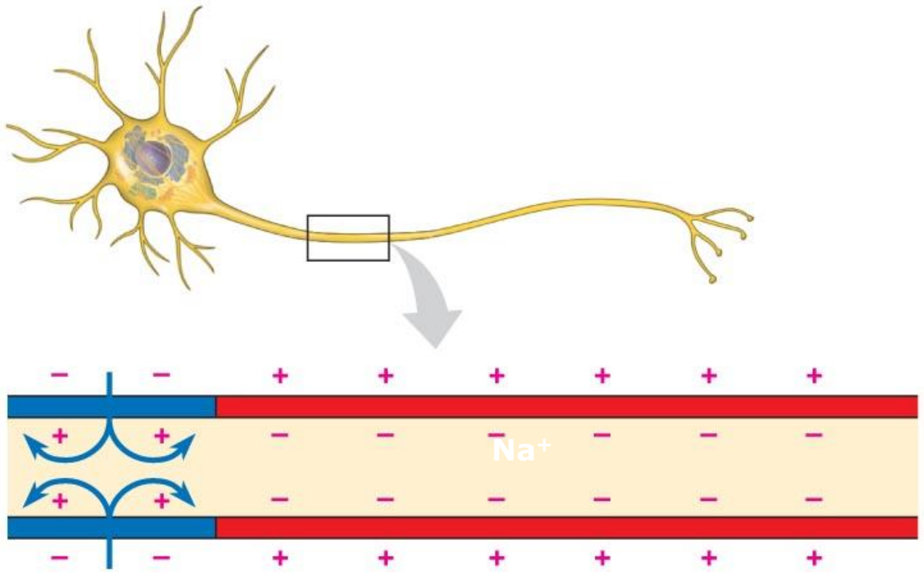
- A strong stimulus results in a massive change in membrane voltage called an **action potential**

Generation of Action Potentials:

- A neuron can produce hundreds of action potentials per second
- There are **several ways to reflect the strength of a stimulus**
  - *Frequency of action potentials* – a weak stimulus initiates only a few action potentials/sec., a strong stimulus initiates many (upper limit because of refractory period)
  - *Duration of a burst of action potentials* – a weak stimulus may give rise to a short burst of pulses in the neuron, a strong stimulus a longer burst
  - *Number & kinds of neurons firing* – The threshold needed to initiate a nerve impulse varies from one neuron to another. Thus a weak stimulus will cause only a few neurons to fire, strong will fire all of these neurons, plus others with higher thresholds.

Conduction of Action Potentials



- An action potential can travel long distances by **regenerating itself along the axon**
- **Inactivated Na⁺ channels behind the zone** of depolarization prevent the action potential from traveling backwards
- **Action potentials travel in only one direction**: toward the synaptic terminals

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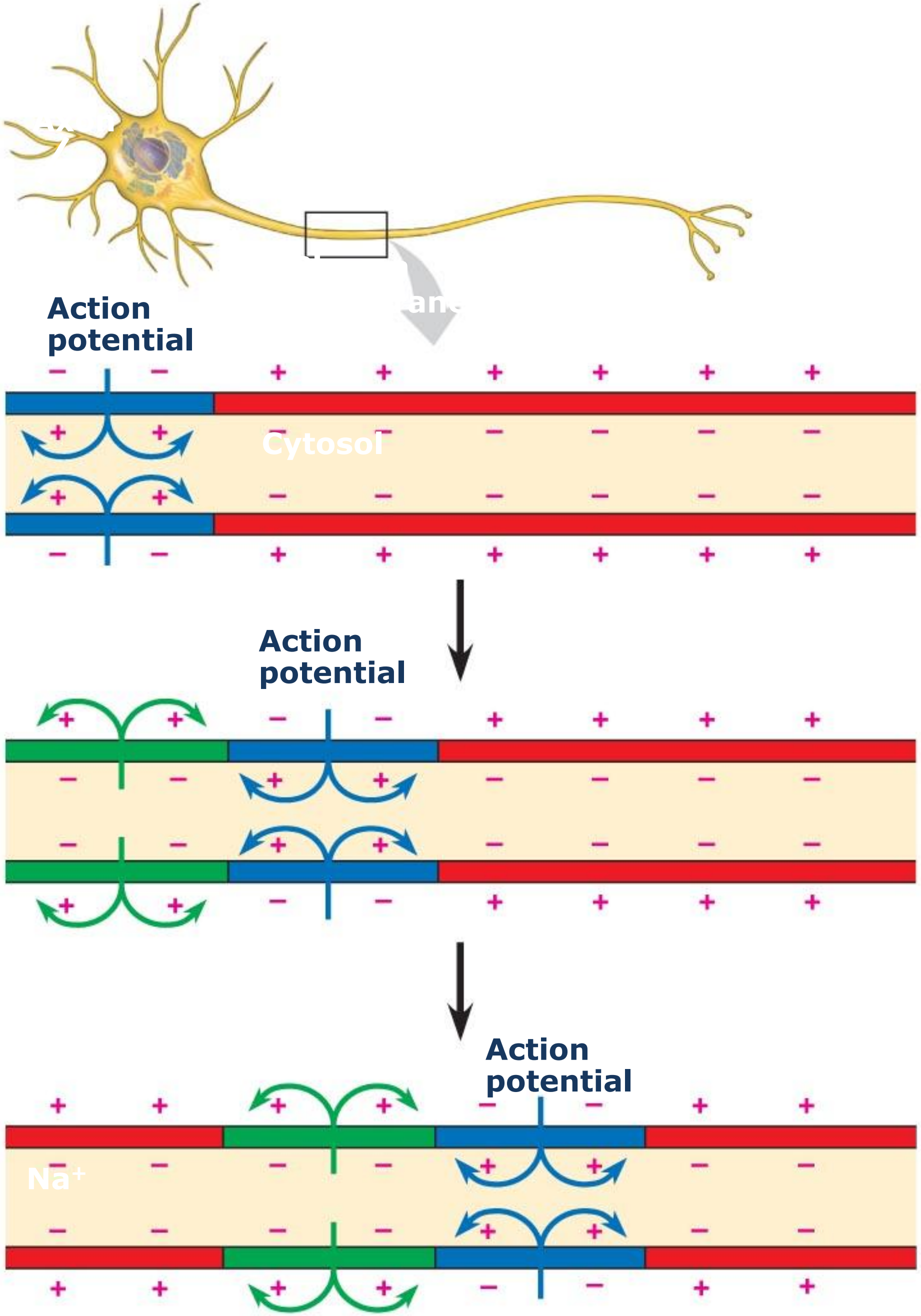
At the site where the action potential is generated, usually the axon hillock, an **electrical current** depolarizes the neighboring region of the axon membrane

The depolarization - repolarization process is repeated in the next region of the membrane. In this way, local currents of ions across the plams membrane cause the action potential to be propagated along the length of the axon



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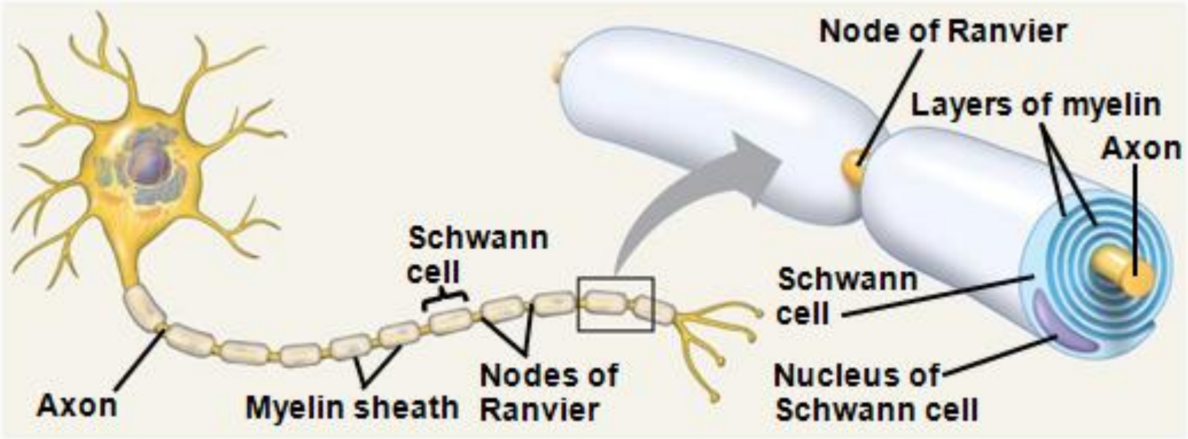
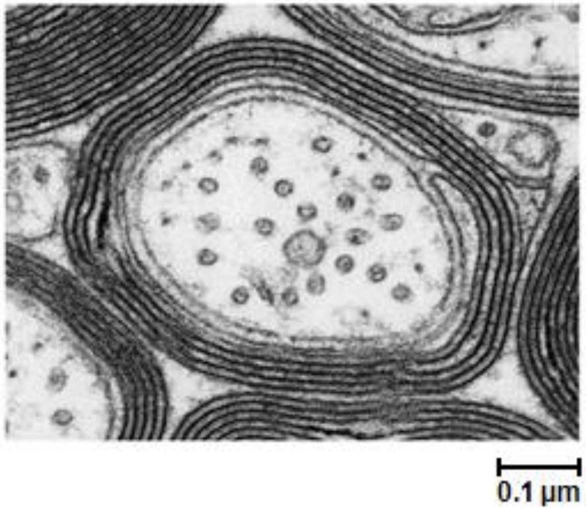
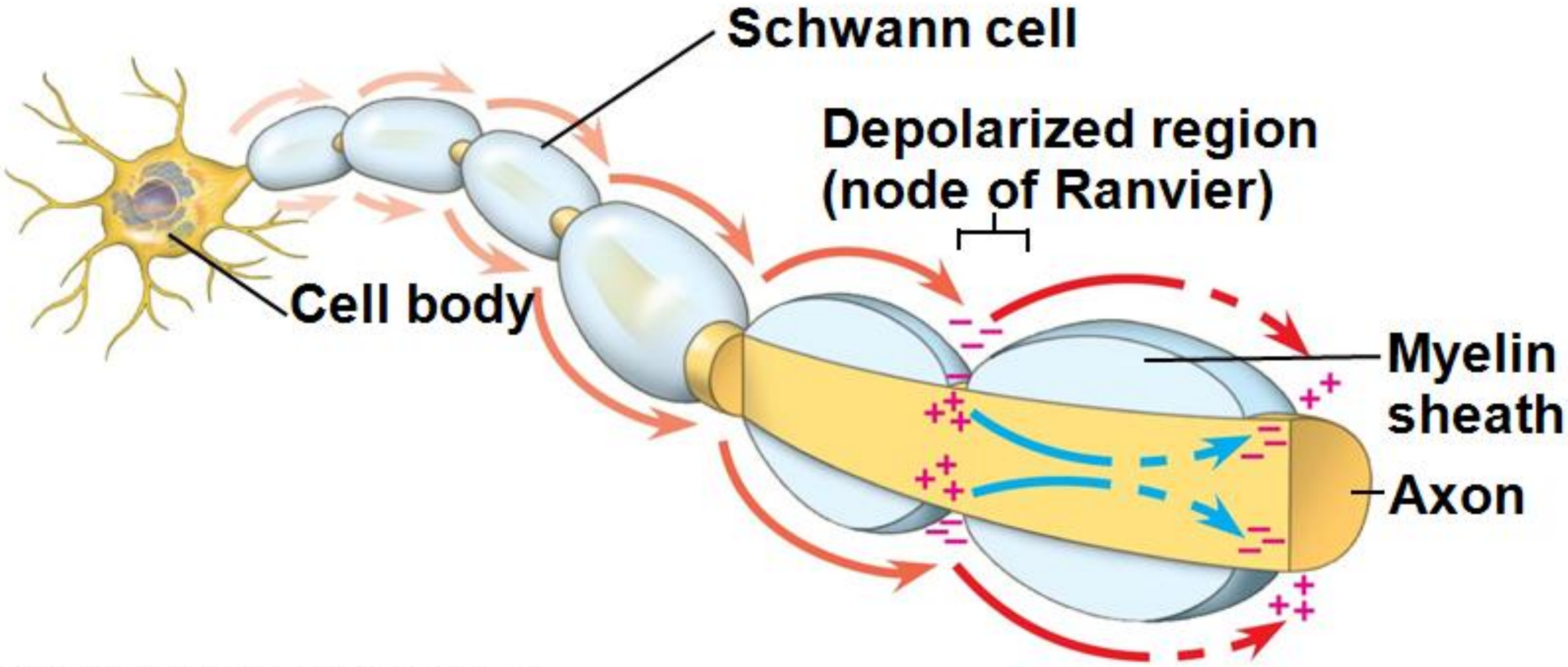
- The speed of an action potential increases with the axon’s diameter
- In vertebrates, axons are insulated by a **myelin sheath**, which causes an action potential’s speed to increase
- Myelin sheaths are made by glia— **oligodendrocytes** in the CNS and **Schwann cells** in the PNS





- Action potentials are formed only at **nodes of Ranvier**, gaps in the myelin sheath where voltage-gated Na+ channels are found
- Action potentials in myelinated axons jump between the nodes of Ranvier in a process called **saltatory conduction**



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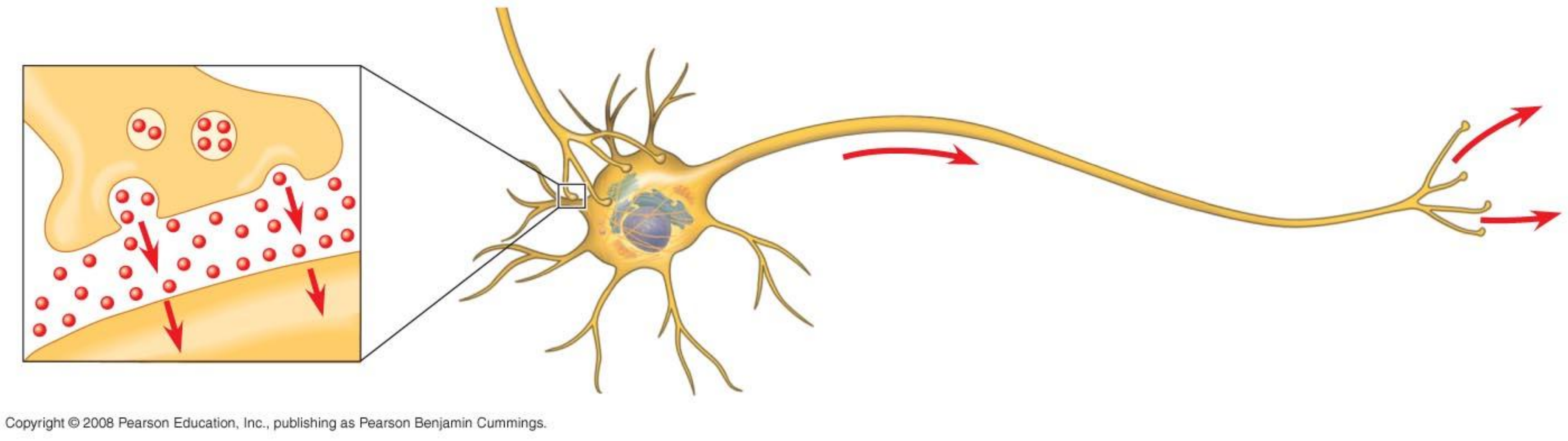
Neurons communicate with other cells at synapses

- At *electrical synapses*, the electrical current flows from one neuron to another
- At *chemical synapses*, a chemical neurotransmitter carries information across the gap junction
- Most synapses are chemical synapses
- The presynaptic neuron synthesizes and packages the neurotransmitter in **synaptic vesicles** located in the synaptic terminal
- The action potential causes the release of the neurotransmitter
- The neurotransmitter diffuses across the **synaptic cleft** and is received by the postsynaptic cell

A **synapse** is a junction between an axon and another cell

The **synaptic terminal** of one axon passes information across the synapse in the form of chemical messengers called **neurotransmitters**



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Information is transmitted from a **presynaptic cell** (a neuron) to a **postsynaptic cell or effector** (a neuron, muscle, or gland cell)

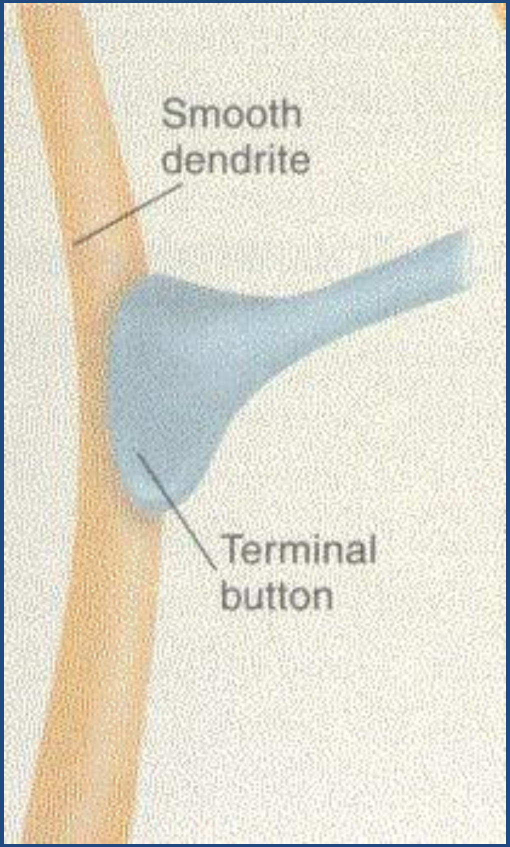
Most neurons are nourished or insulated by cells called **glia**

Types of synapses by binding

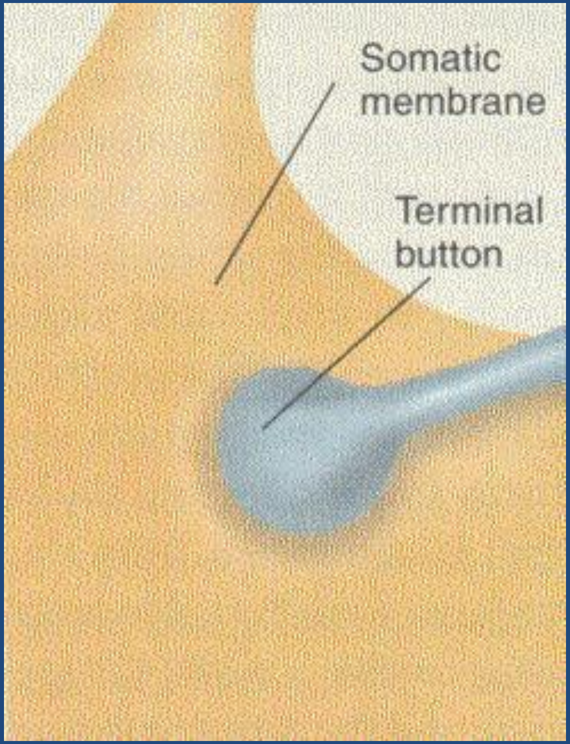
Axodendritic – synapse on the dendrite of the neuron

Axosomatic – synapse on the soma

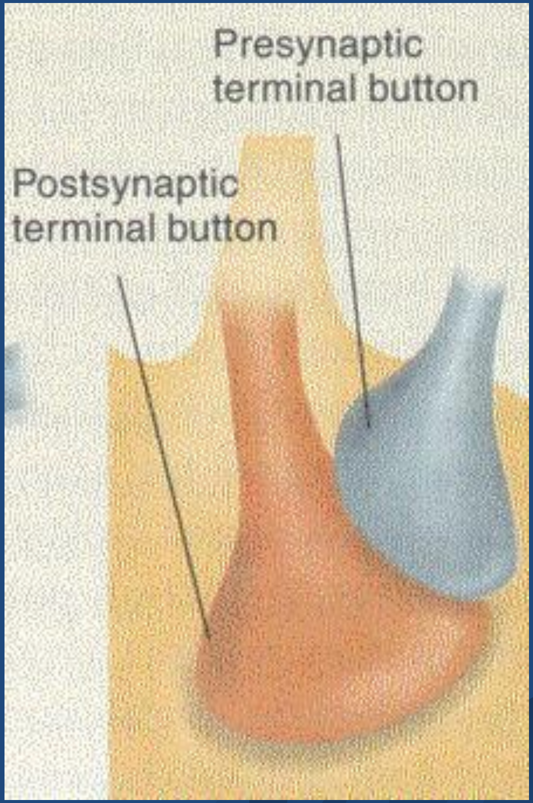
Axoaxonic – synapse on the axon



Axodendritic



Axosomatic



Axoaxonic

Synapse

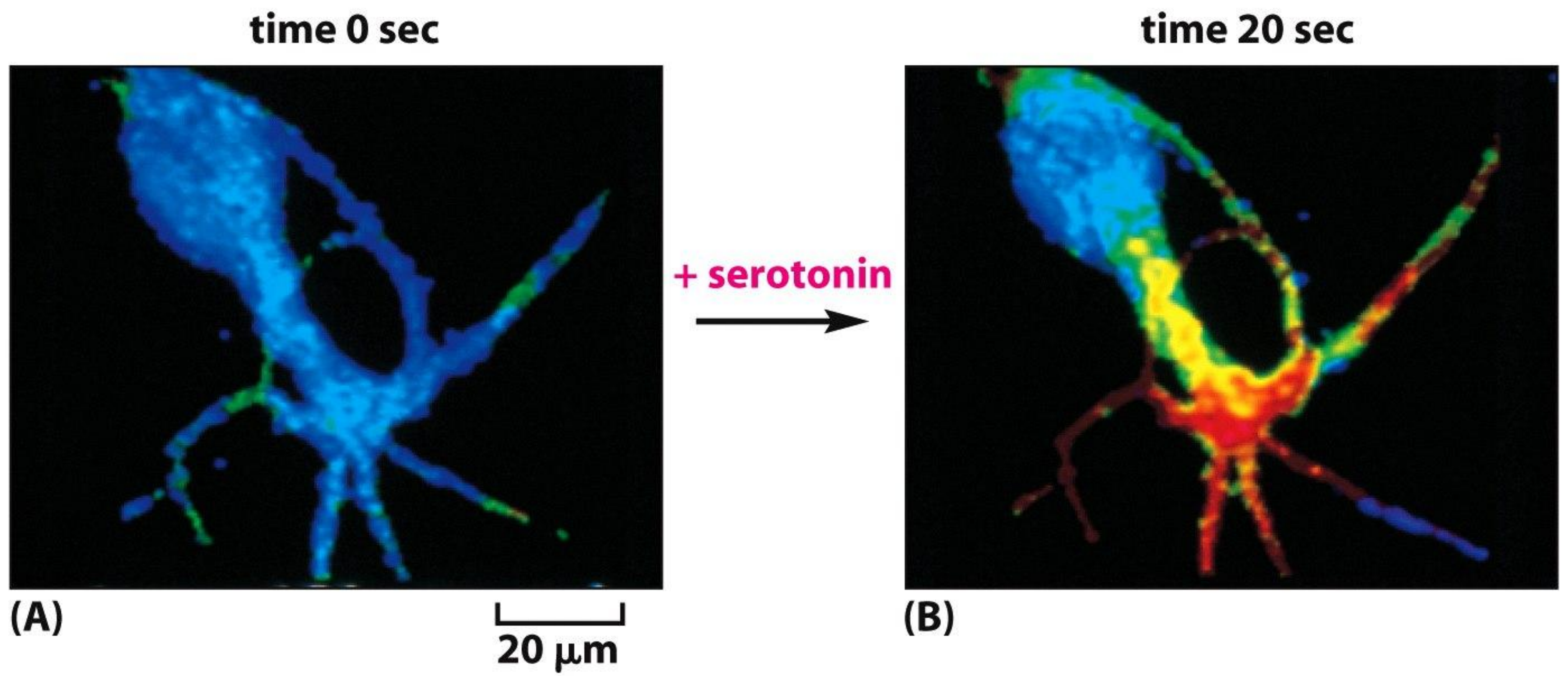
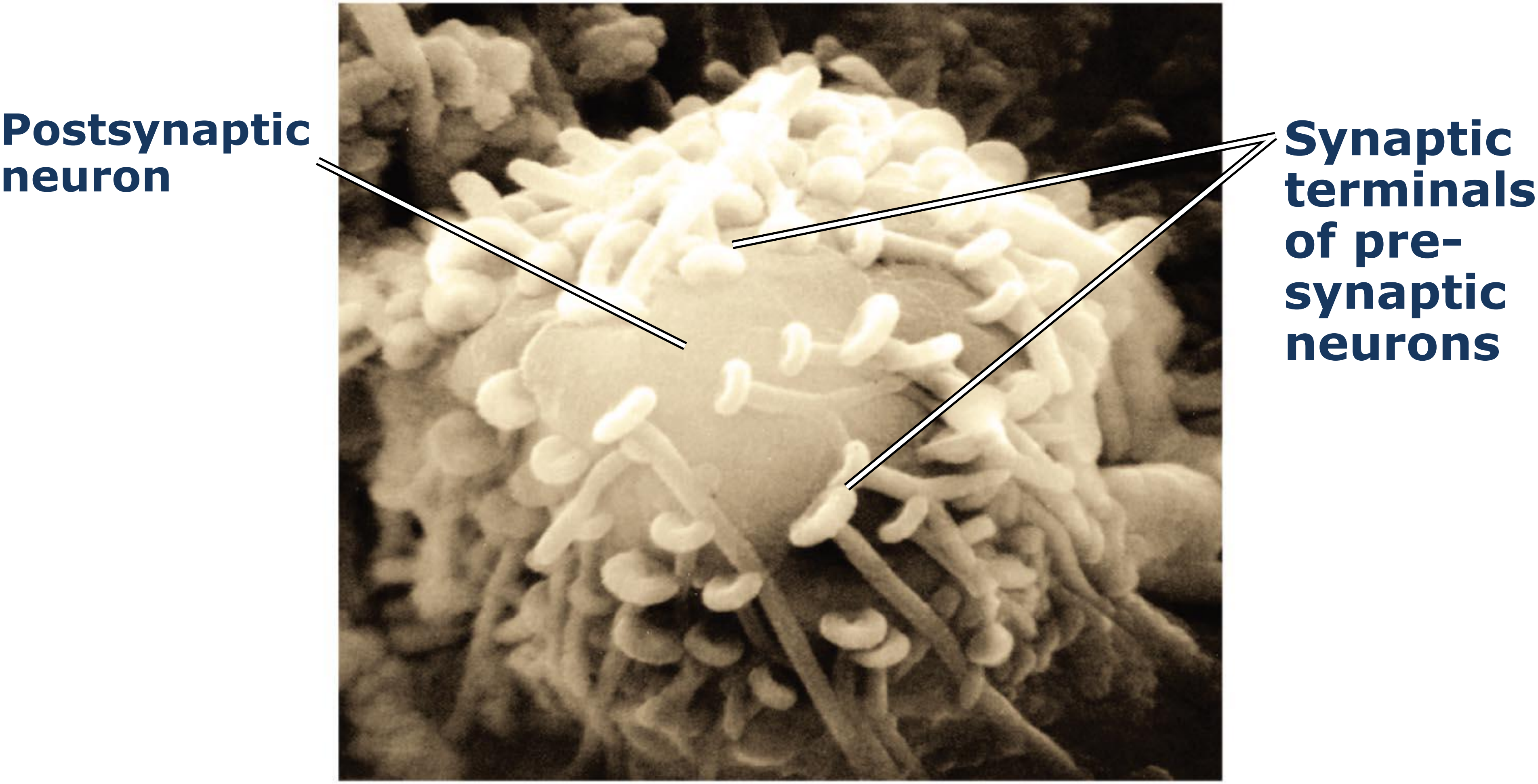


Figure 15-33 Molecular Biology of the Cell 5/e (© Garland Science 2008)

A cultured nerve cell responding to the neurotransmiter serotonin. Serotonin acts through a GPCR and activates cAMP synthesis. The cells express a fluorescent proteins that changes its fluorescence upon binding of cAMP. Blue indicate low concentration of cAMP, yellow – intermediate and, red a high concentration of cAMP.



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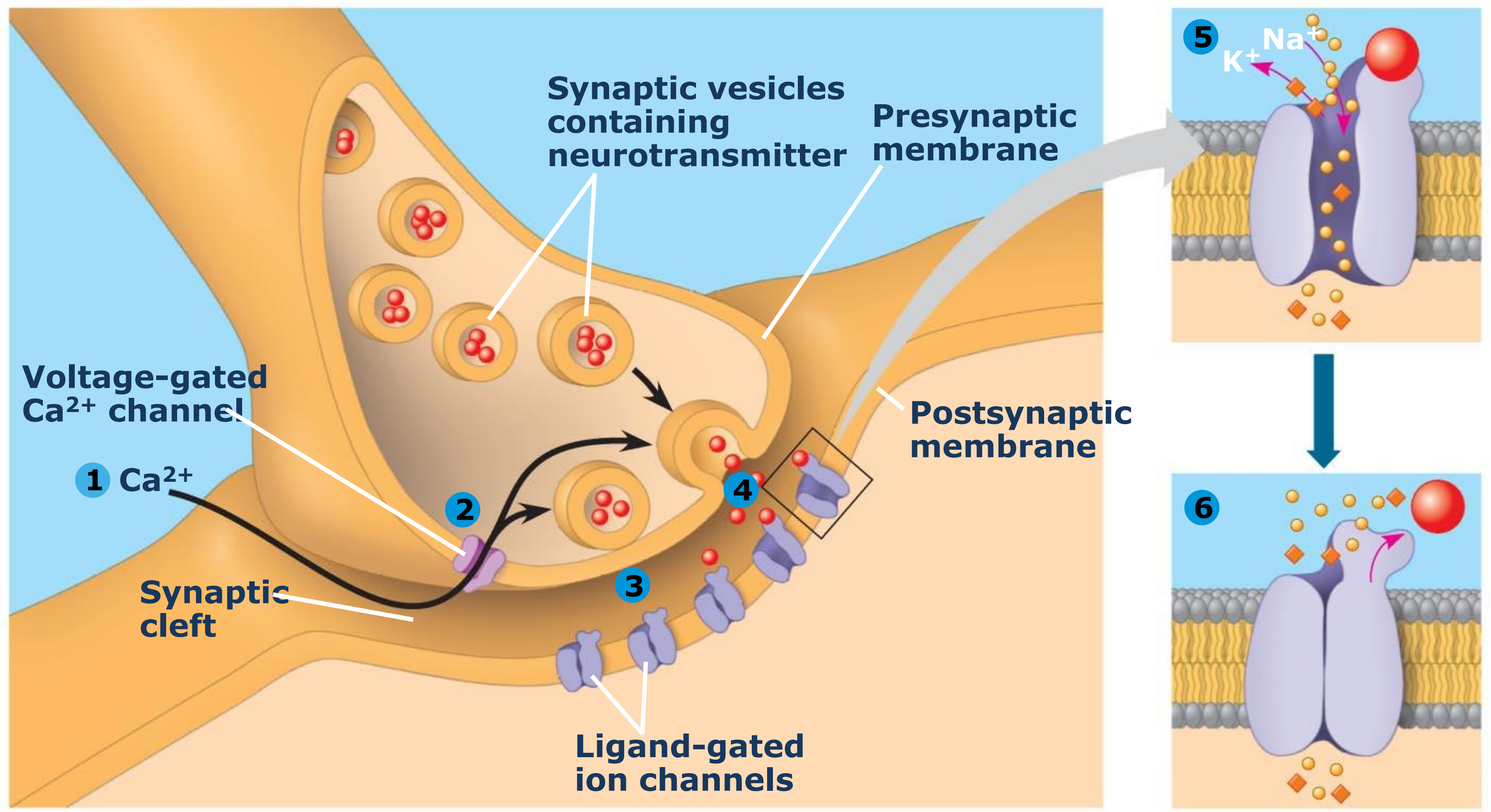
Synaptic vesicles containing neurotransmitter
Presynaptic membrane
Voltage-gated Ca^{2+} channel
1 Ca^{2+}
2
Synaptic cleft
3
4
Postsynaptic membrane
Ligand-gated ion channels
5
K^+
Na^+
6

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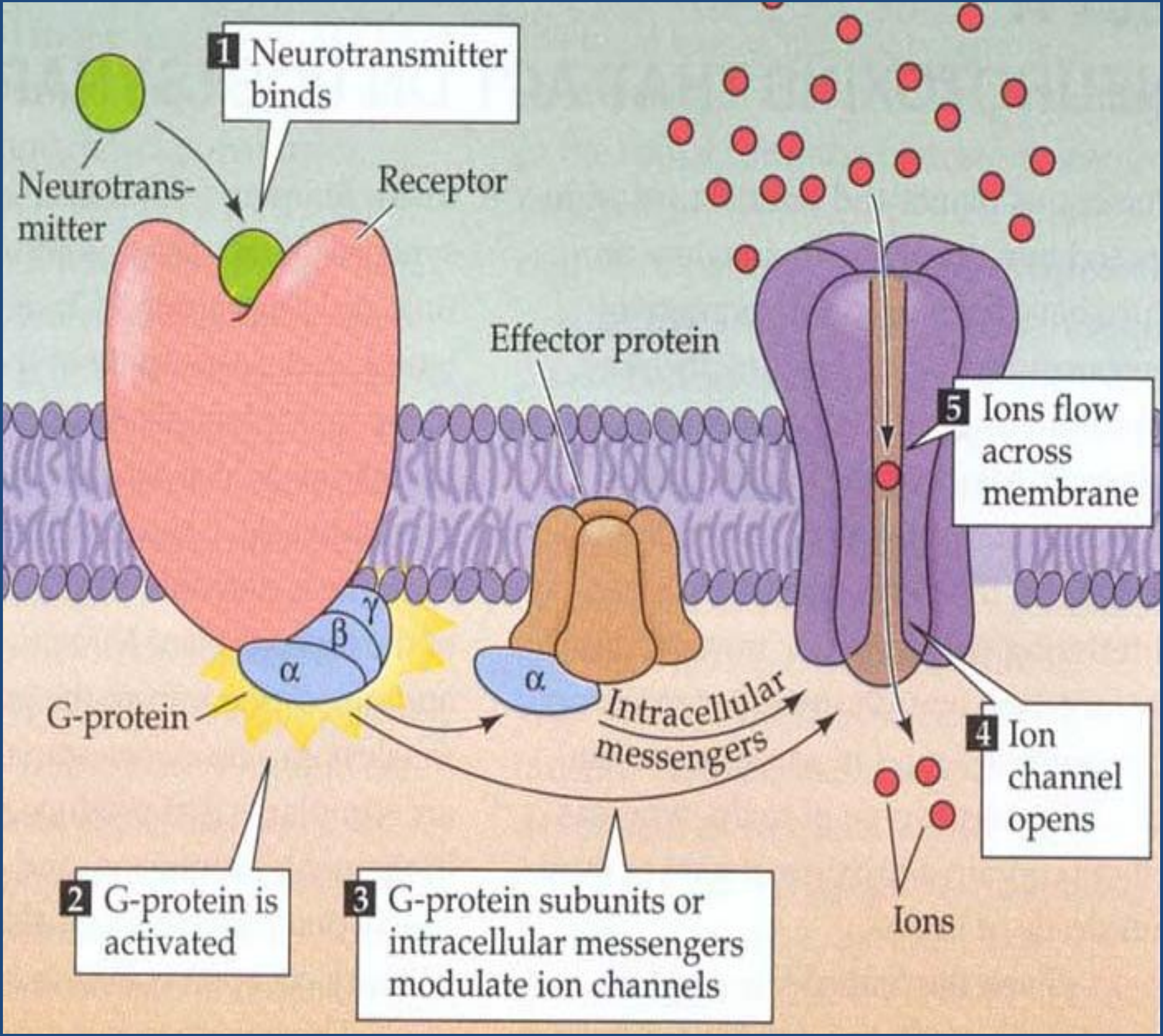
Generation of Postsynaptic Potentials

- Direct synaptic transmission involves binding of neurotransmitters to ligand-gated ion channels in the postsynaptic cell
- Neurotransmitter binding causes ion channels to open, generating a *postsynaptic potential*
- Postsynaptic potentials fall into two categories:
  - **Excitatory postsynaptic potentials (EPSPs)** are depolarizations that bring the membrane potential toward threshold
  - **Inhibitory postsynaptic potentials (IPSPs)** are hyperpolarizations that move the membrane potential farther from threshold

- After release, the neurotransmitter
  - May diffuse out of the synaptic cleft
  - May be taken up by surrounding cells
  - May be degraded by enzymes

1 Neurotransmitter binds
Neurotransmitter
Receptor
Effector protein
5 Ions flow across membrane
γ
β
α
α
G-protein
Intracellular messengers
4 Ion channel opens
Ions
2 G-protein is activated
3 G-protein subunits or intracellular messengers modulate ion channels

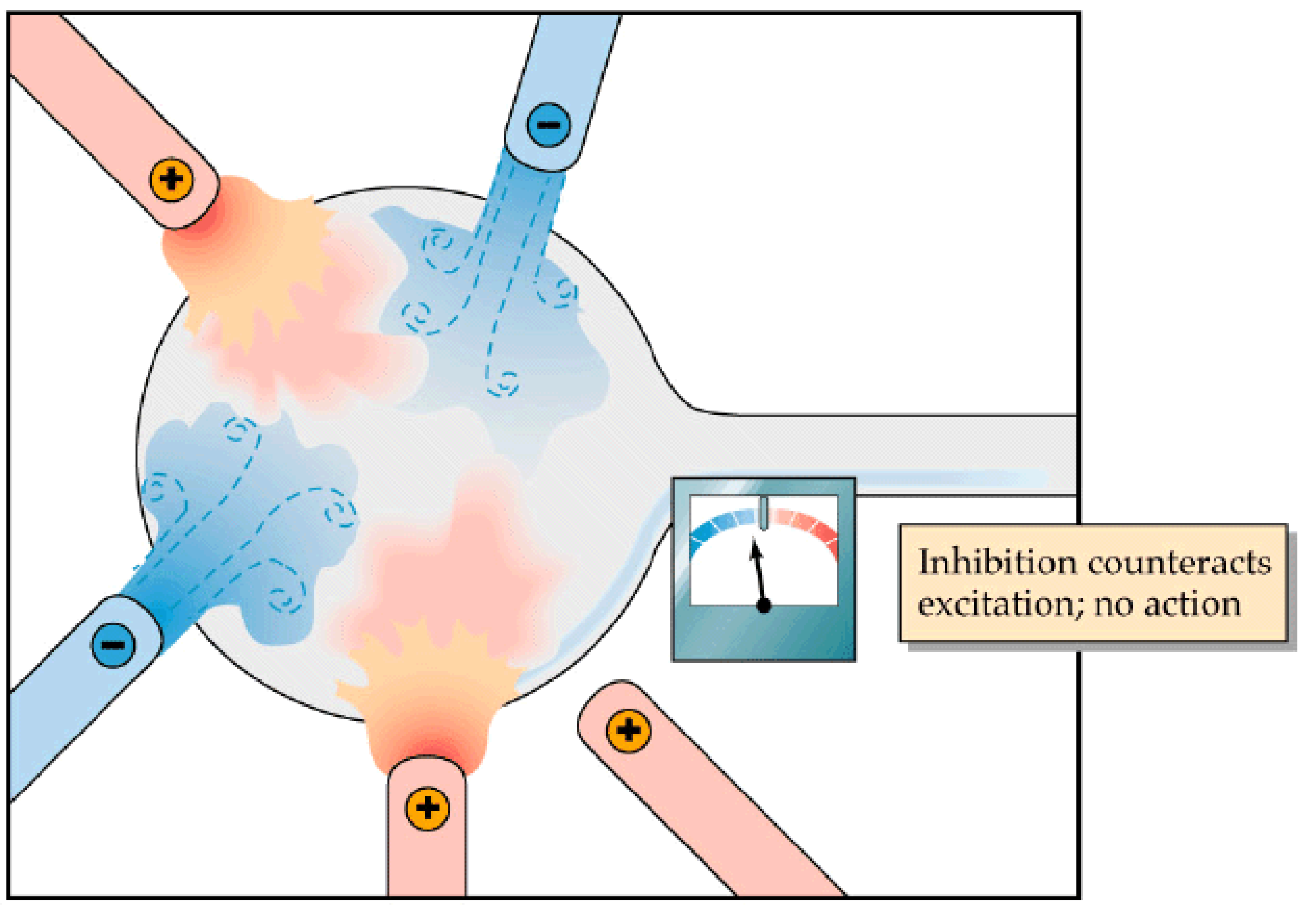
$$\left.\begin{array}{l}\textbf{Glucagon}\\ \beta\textbf{-adrenaline}\\ \textbf{ACTH}\end{array}\right\}\xrightarrow{\oplus}\alpha_{s}\rightarrow\textbf{AC}\uparrow$$

$$\left.\begin{array}{l}\alpha\textbf{-adrenaline}\\ \textbf{angiotensin II}\\ \textbf{acetylcholine}(M_{2}\ M_{4})\end{array}\right\}\xrightarrow{\oplus}\alpha_{i}\rightarrow\textbf{AC}\downarrow$$

GF release inhibitory factor

Neural integration

Spatial integration: equal excitatory and inhibitory input will cause no change



Inhibition counteracts excitation; no action

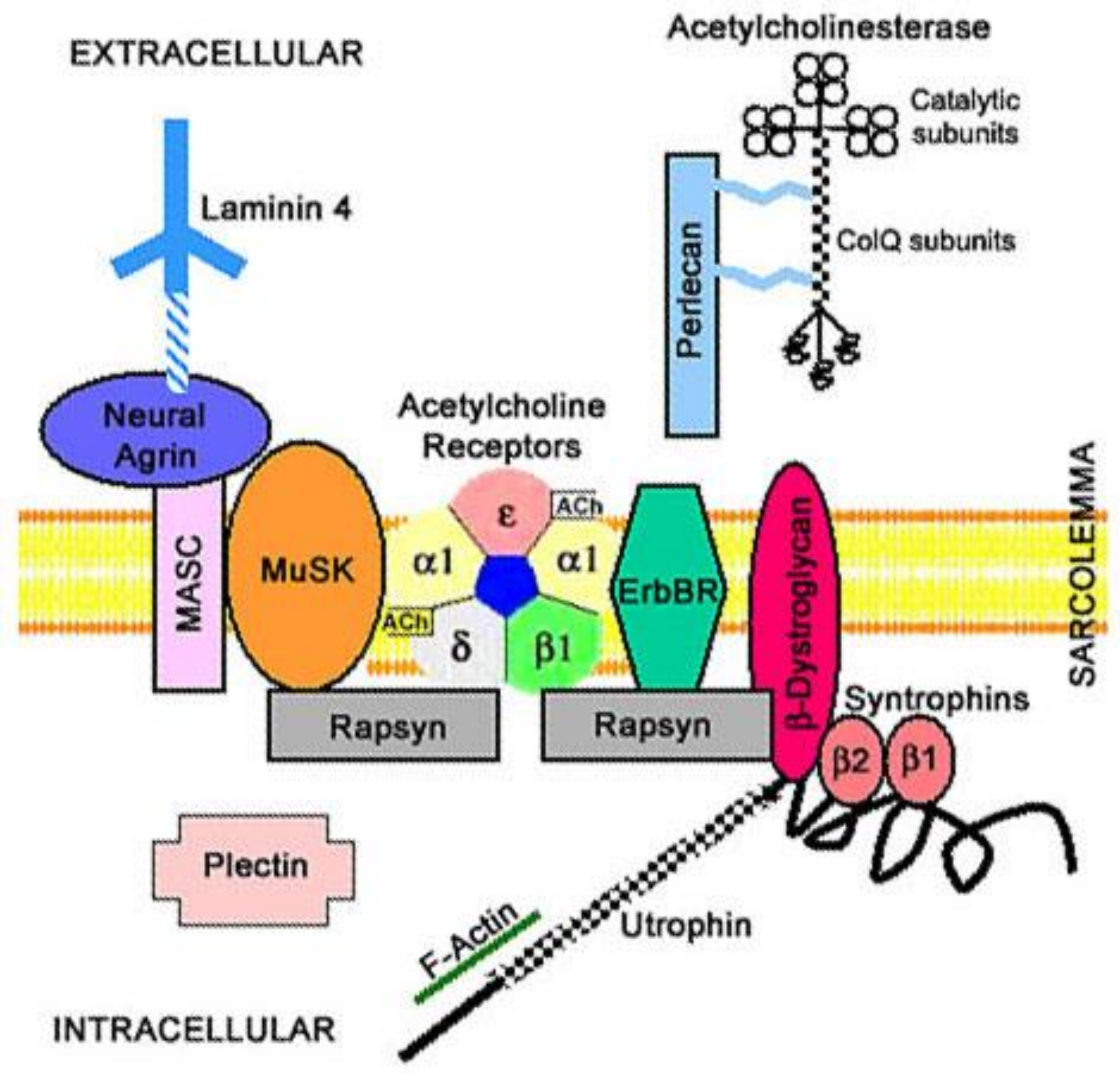
Neurotransmitters

1. **Acetylcholine (ACh)** is involved in both learning and memory and muscle movement
2. **Dopamine** impacts our arousal and mood states, thought processes, and physical movement
3. **Serotonin** and **norepinephrine** are neurotransmitters involved in levels of arousal and mood, and play a major role in mood disorders such as depression
4. **GABA** is the main inhibitory neurotransmitter in the nervous system; **glutamate** is the main excitatory neurotransmitter
5. **Endorphins** are a group of neurotransmitters that are involved in pain perception and relief

Autoreceptors

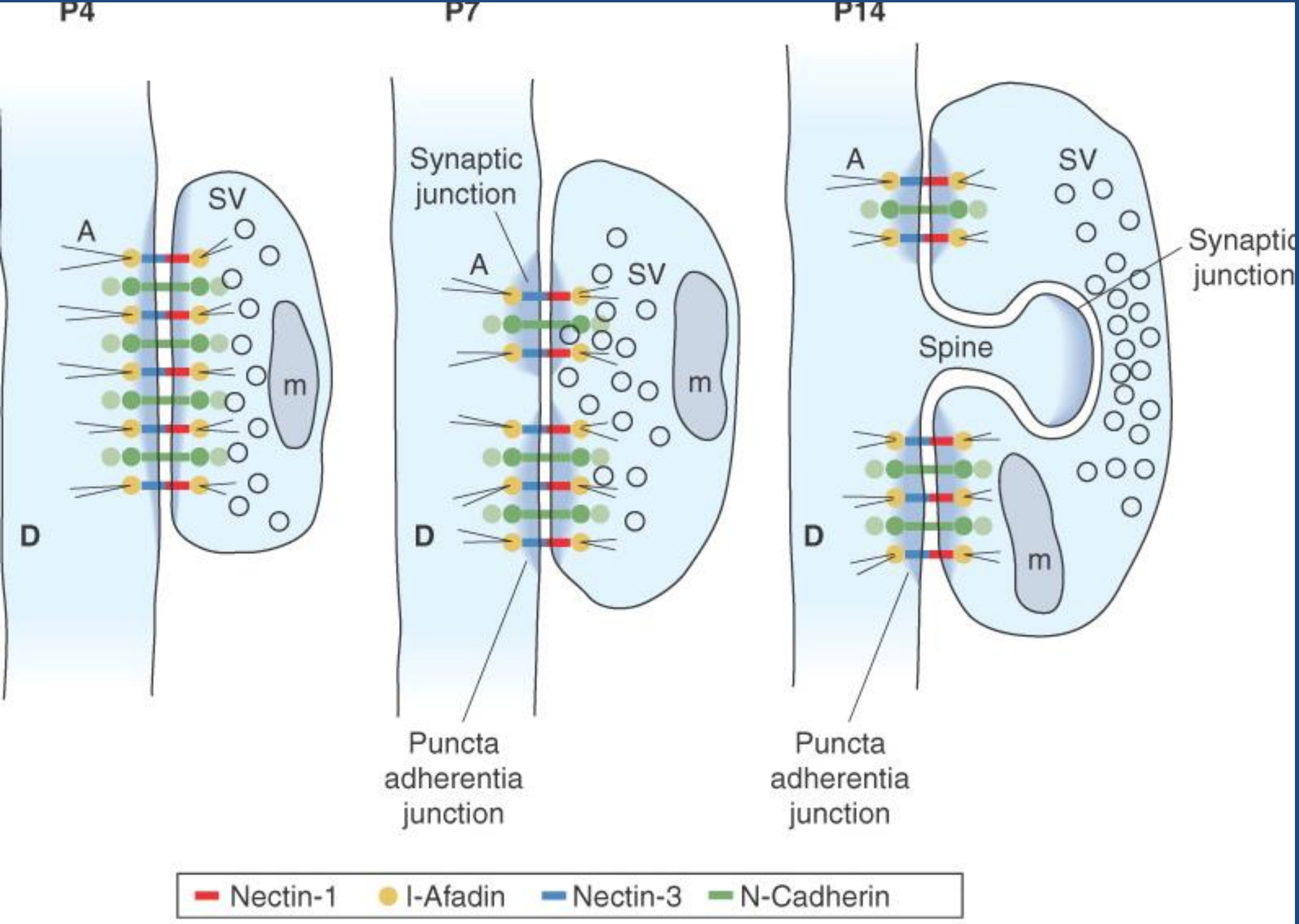
- autoreceptors respond to neurotransmitters they produce
- regulate synthesis and release of other transmitters
- metabotropic
- usually inhibitory – may control amount of neurotransmitter released

Synapse at the neuromuscular junction

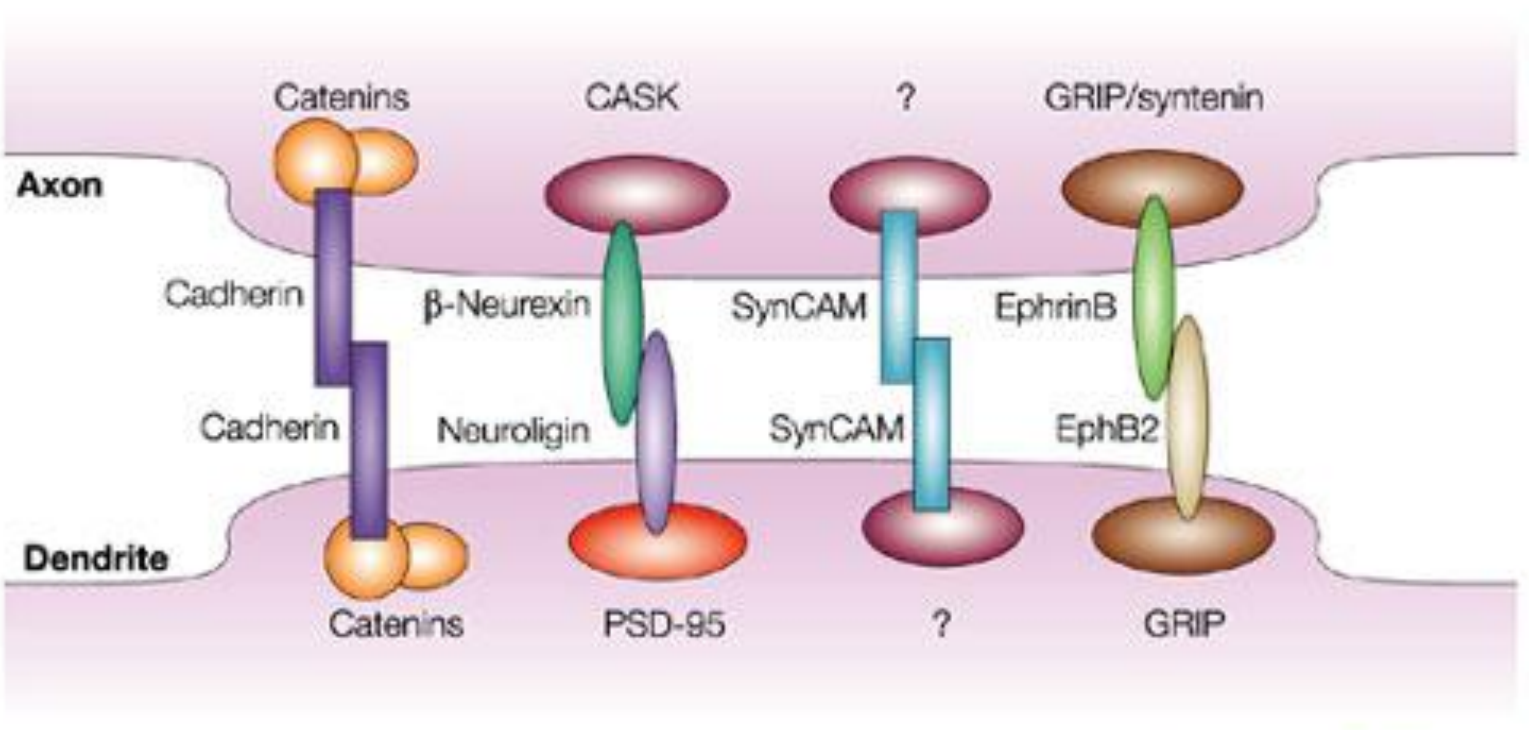


The Nectin-Afadin Adhesion System in Synaptogenesis in Hippocampal Pyramidal Neurons (next slide)

- Nectin-afadin system organizes adherens junctions cooperatively with the cadherin-catenin system in hippocampal pyramidal neurons.
- Nectin: an IgG-like adhesion molecule.
- Afadin: an actin-filament binding protein that connects nectin to the actin cytoskeleton.
- During development, nectin-1 and -3 localize at both puncta adherentia junctions and mechanically anchor at synaptic junctions.
- Note that the nectin-afadin and the cadherin-catenin systems co-localize around the active site zones throughout development.

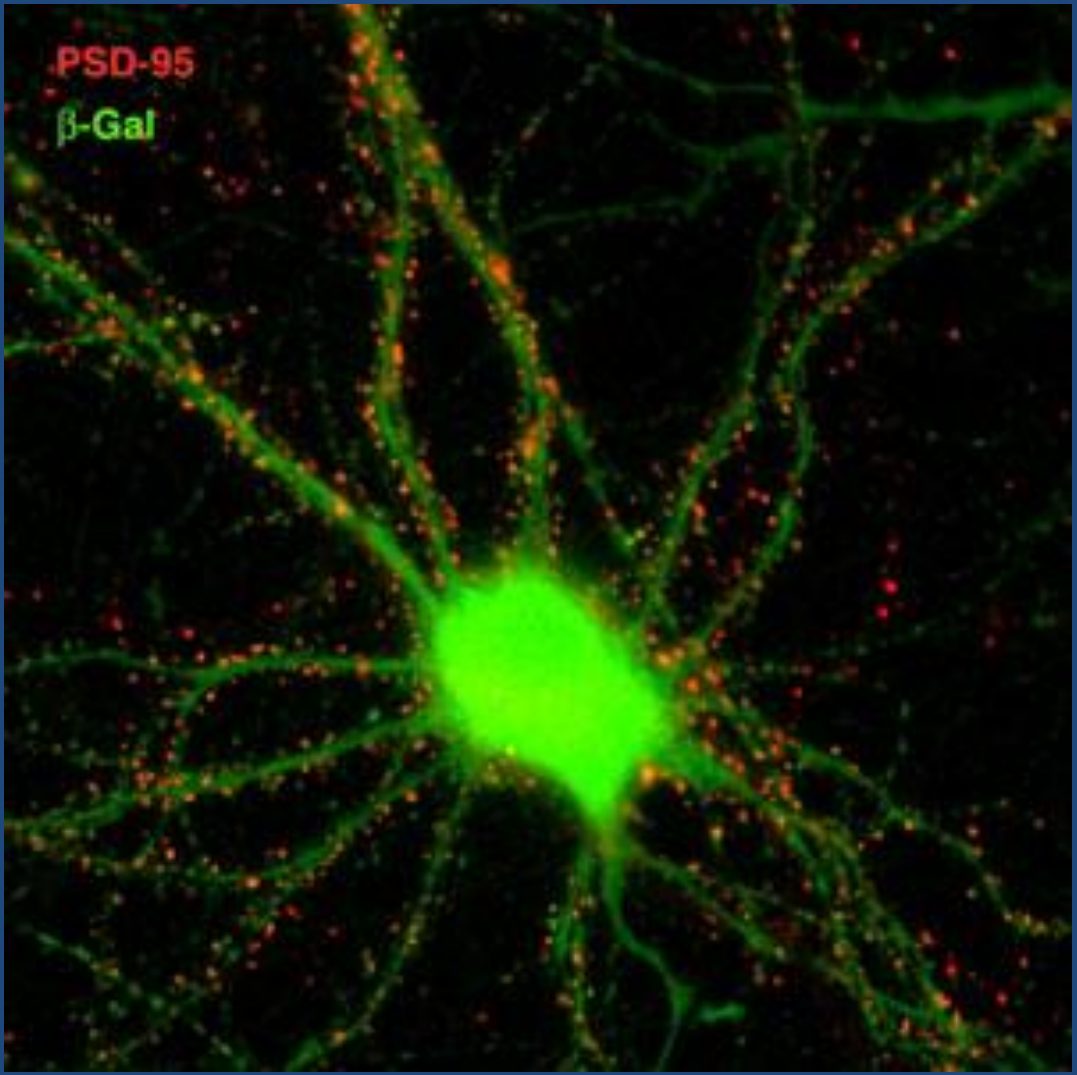

P4
P7
P14
A
SV
m
D
A
Synaptic junction
SV
m
D
Puncta adherentia junction
A
SV
Synaptic junction
Spine
m
D
Puncta adherentia junction
🟥 Nectin-1
● I-Afadin
🟦 Nectin-3
🟩 N-Cadherin

Trans-synaptic protein interactions implicated in synaptic contact/adhesion & synapse development: Some players



Nature Reviews | Molecular Cell Biology

Homophilic interactions: The carboxy-terminal cytoplasmic tails of -neurexin, neuroligin, EphB2, ephrinB and SynCAM (synaptic cell-adhesion molecule) bind to specific PDZ and ZO-1-domain-containing proteins, which can assemble large protein complexes that are associated with the cell-surface membrane protein.
Zheng Li & Morgan Sheng 2003



Rat **hippocampal neuron** in culture expressing beta-Gal to visualize the dendrites, and immunostained for beta-Gal (green) and **PSD-95** (red), a protein enriched in postsynaptic structures, the dendritic spines.